

**OXYGEN KINETICS AND ENERGY EXPENDITURE IN  
FULMINANT HEPATIC FAILURE AND DURING LIVER  
TRANSPLANTATION**

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## DECLARATION

I declare that this thesis was my own composition. The majority of the work was carried out between 1995 and 1996 whilst in the post of Clinical Fellow in Anaesthesia for Transplantation in the Scottish Liver Transplant Unit, Royal Infirmary, Edinburgh.



Timothy Walsh  
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For Claire, Sam, and Jonathan

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## ABSTRACT

This thesis examines aspects of oxygen transport and uptake in patients with acute and chronic liver disease with specific reference to the management of fulminant hepatic failure (FHF) and the intraoperative management of patients undergoing liver transplantation.

A prospective randomised controlled study was carried out in patients with FHF evaluating the effect of the drug N-acetylcysteine on  $\text{DO}_2$ ,  $\text{VO}_2$ , and tissue oxygen extraction. A previous study showed that this drug increased all of these oxygen kinetic variables, which was considered of therapeutic benefit. The present study showed that this earlier finding was an artifact related to the method of calculating oxygen consumption (the Fick method). This method produced unreliable results in patients with FHF because it was inaccurate, non-reproducible, the relation between  $\text{DO}_2$  and  $\text{VO}_2$  was subject to mathematical coupling error. No clinically significant improvements in any oxygen kinetic variables were observed after N-acetylcysteine administration, even when followed for a prolonged period. Variable effects on cardiovascular parameters were found, but overall no differences from the control group were demonstrated. No relationship was found between plasma N-acetylcysteine concentrations and clinical response.

A prospective study examining energy expenditure and the acute phase response was carried out in patients with FHF. Energy expenditure was increased by approximately 20-25% in FHF in comparison with spontaneously breathing healthy volunteers and physically anhepatic patients with chronic liver disease studied during liver transplantation. Plasma  $\text{TNF}\alpha$ , IL-6, and C-reactive protein were measured. These were significantly elevated in comparison with healthy controls in keeping with a significant acute phase response. The study indicated hypermetabolism during severe FHF despite the loss of functioning liver cell mass and the effects of sedation, analgesia, and mechanical ventilation. This was most likely attributable to a systemic inflammatory response.

In patients undergoing liver transplantation indirect calorimetry was used to examine changes in metabolic rate and pulmonary physiology following graft

reperfusion. Significant changes in metabolic rate, oxygen transport, and acid-base balance were demonstrated the factors which influence these changes were discussed. The use of the piggyback surgical technique was associated with greater metabolic stability than the use of venovenous bypass.

A prospective observational study compared the two methods for managing the anhepatic phase of liver transplantation, namely venovenous bypass or the piggyback surgical technique. This study demonstrated higher cardiac output,  $\text{VO}_2$ , and blood temperature during the anhepatic phase with the piggyback surgical technique. This suggested better preservation of tissue oxygenation with this approach, which may translate into improved postoperative function.

Two techniques of graft reperfusion, namely via the portal vein or the hepatic artery, were compared in another prospective observational study. This study indicated that the increase in  $\text{VO}_2$  after reperfusion occurred more slowly when the hepatic artery was used, but was accompanied by a slower release of acid load into the circulation and less requirement for vasopressor support. Reperfusion via the hepatic artery may therefore be preferable in the patient at risk of haemodynamic or cerebral decompensation following reperfusion, although further studies are required to ensure graft outcome is equivalent with both techniques.

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### INTRODUCTION

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#### OXYGEN

Oxygen is essential to life. This extremely reactive chemical is capable of reaction with most constituents of cells. Using oxygen organisms are able to oxidise more completely the molecules they ingest, thereby improving the efficiency of energy production through the process of respiration. Respiration drives the synthesis of adenosine triphosphate (ATP) which acts as energy substrate for biological reactions. The reactivity of oxygen make it at once essential and potentially toxic to cells. Oxygen derived free radicals damage cellular constituents and require rapid neutralisation. With evolution oxygen balance has become a complex process by which oxygen is taken up within lungs and transported within blood via the cardiovascular system to individual organs and tissues, from which it moves into individual cells. Within cells oxygen takes part in oxidative phosphorylation which generates ATP. Each of these processes is under complex physiological control which, during critical illness, may become deranged resulting in cellular dysfunction and, ultimately, death. A primary goal of critical care research is to accurately measure and understand the physiology and pathophysiology of oxygen in humans.

#### MEASUREMENT OF OXYGEN CONSUMPTION

There are two approaches to determining oxygen consumption in humans. Firstly, oxygen uptake by the body can be measured by techniques which examine gas exchange across the lungs. Secondly, oxygen consumption can be calculated using the Fick principle.

#### Gas exchange Techniques

Oxygen consumption can be calculated by measuring the oxygen content of inspired and expired gas according to the equation:

$$VO_2 = (VI \times FIO_2) - (VE \times FEO_2) \quad [1]$$

where VI and VE are inspired and expired volumes, and FIO<sub>2</sub> and FEO<sub>2</sub> are inspired and expired oxygen fractions respectively. The accurate and rapid measurement of gas fractions is possible with current technology such as the paramagnetic oxygen analyser and infrared carbon dioxide analyser. It remains technically difficult to determine gas volumes with the accuracy necessary for clinical measurements, particularly problematic is the detection of differences between inspired and expired gas volumes.

A common approach in gas exchange measurements is to determine VE and then recalculate VI using Haldane's hypothesis, which assumes all metabolically inert gases (principally nitrogen) are at a steady state.

$$\text{Thus: } VI \times FIN_2 = VE \times FEN_2$$

$$\text{and: } VI = VE(FEN_2/FIN_2) \quad [2]$$

From [1] and [2]:

$$VO_2 = VE[(FIO_2 \times FEN_2/FIN_2) - FEO_2] \quad [3]$$

If inspired gas contains no gases other than O<sub>2</sub> and N<sub>2</sub>:

$$FIN_2 = 1 - FIO_2 \quad [4]$$

$$\text{and } FEN_2 = 1 - FEO_2 - FECO_2 \quad [5]$$

Combining [3], [4], and [5] gives:

$$VO_2 = VE \times [(FIO_2 \times (1 - FEO_2 - FECO_2)/(1 - FIO_2)) - FEO_2] \quad [6]$$

The application of Haldane's principle to transform the measurement of  $\text{VO}_2$  from a requirement to measure both inspired and expired volumes to a formula requiring measurement of gas fractions and expired volume alone (often termed the Haldane transformation) allows the use of various "open circuit" techniques of determining  $\text{VO}_2$ . The simplest of these is the Douglas bag method with which all expired gas is collected for a timed period from the breathing circuit. The gas is then sampled for its oxygen and carbon dioxide concentration which are measured. The collected gas volume is then determined together with temperature and ambient barometric pressure. The volume is then corrected to standard dry temperature and pressure and  $\text{VO}_2$  calculated using the above formula. This method is time consuming and the potential for measurement errors is large such that it is not suitable for routine use in ventilated patients. In the 1970s and 1980s many "metabolic carts" were developed which sought to automate this process. These were developed primarily for metabolic studies in healthy spontaneously breathing subjects and are frequently called *indirect calorimeters* because they calculated energy expenditure from  $\text{VO}_2$  and  $\text{VCO}_2$ . The need to determine  $\text{VO}_2$  and energy expenditure in critically ill ventilated patients led to their adaptation and modification for this setting.

Initial studies using metabolic carts in the critically ill suggested that this method was inaccurate. Inaccuracies occurred because of methodological problems which were not addressed with early devices.

#### *Methodological problems associated with indirect calorimetry.*

*Influence of  $\text{FIO}_2$ :* In the Haldane transformation equation the measured value for  $\text{FIO}_2$  is involved in divisional, multiplicative, and subtractive calculations (equation 6). Thus small errors in the measurement of  $\text{FIO}_2$  and  $\text{FEO}_2$  are propagated and multiplied in the final calculation. If a subject is breathing room air errors are likely to be relatively small because the  $\text{FIO}_2$  is constant and the difference between  $\text{FIO}_2$  and  $\text{FEO}_2$  is relatively large. In ventilated patients in whom a high  $\text{FIO}_2$  is required the

difference between  $FIO_2$  and  $FEO_2$  may be small. This, combined with small fluctuations in  $FIO_2$  which occur with the oxygen/air blenders of some ventilators, may cause considerable errors (Welch and Pedersen 1981, Ultman and Bursztein 1981, Browning et al 1982). Errors of this type can be reduced by the presence of mixing chambers after the oxygen blenders and/or prior to analysing expired gas mixtures. The development of rapid response oxygen analysers has also improved accuracy by enabling averaging of many data points, and the virtually simultaneous measurement of both inspired and expired gases.

*Presence of gas leaks:* Gas leaks generally result in an underestimation of  $VO_2$  and are particularly problematic. The commonest site is around the endotracheal tube, particularly in children, but leaks from other parts of the breathing system, from chest drains, or from within the indirect calorimeter itself can cause significant errors (Bracco et al 1995, Selby et al 1995). Leaks may be difficult to detect but can represent a significant proportion of the expired gas volume, particularly in children or if airway pressures are high as occurs in ARDS and during the application of positive end-expiratory pressure (PEEP).

*Humidity:* Measurements of gas volume are expressed under standard conditions which include the absence of humidity. Measurements of gas fractions usually assume complete drying of gas which may be difficult in ventilated patients, particularly when humidifiers are used. The presence of water in gas analysers also alters their accuracy. Problems associated with humidity have been solved in most modern metabolic monitors by including water permeable tubing and water traps in the circuits.

*Lack of a steady state:* The Haldane transformation makes the assumption that there is no difference between inspired and expired nitrogen fractions. Following a change in  $FIO_2$  inverse alterations in  $FIN_2$  occur, and as body stores of nitrogen are considerable several minutes are required until a steady state is reestablished. Changes in alveolar ventilation also disrupt the steady state for nitrogen although the errors are small and shortlived.

Significant errors in the measurement of  $\text{VCO}_2$  occur if the steady state for carbon dioxide is disrupted. This also affects the accuracy of  $\text{VO}_2$  measurements because expired carbon dioxide fractions are required in the Haldane transformation calculation. A typical adult has carbon dioxide stores of approximately 16 litres in the body which exist in multiple forms and in many different biological compartments (Nunn 1977). If a change in alveolar ventilation occurs it may take 30-60 minutes for complete reequilibration of carbon dioxide stores to occur (Henneberg et al 1987, Taskar et al 1995). Although this is a multiexponential process, most of which occurs during the initial minutes, significant inaccuracy in  $\text{VO}_2$  may occur during this period. Sudden alterations in acid-base balance alter carbon dioxide stores which can alter the steady state resulting in inaccuracy, although this is difficult to quantify. Finally, changes in cardiac output, and therefore tissue perfusion, may alter gas stores in the body although there are no studies which have attempted to quantify the magnitude of these changes and their effect on  $\text{VO}_2$  measurements by indirect calorimetry.

*Interference of other gases:* The Haldane equation assumes the absence of other gases. Thus the presence of volatile anaesthetics, or other gases such as nitric oxide may significantly reduce accuracy (Aukberg et al 1985). Many gases also interfere with the function of gas analysers.

### **The Reverse Fick Method**

The Fick principle, stated originally in 1870, is widely used to calculate physiological variables which are difficult to measure directly. It states that the amount of a substance taken up by an organ, or by the whole body, per unit of time is equal to the arterial level of the substance minus the venous level, times the blood flow. This principle was classically applied to the measurement of cardiac output, by measuring oxygen uptake by the lungs and sampling arterial and venous blood, but the development of the pulmonary artery catheter in the 1960s, and specifically the Swan-Ganz catheter in the early 1970s, resulted in the “reversal” of the principle to back-

calculate oxygen consumption:

$$VO_2 = \text{cardiac output} \times (\text{arterial oxygen content} - \text{mixed venous oxygen content})$$

With this methodology cardiac output is usually measured using the thermodilution technique with a pulmonary artery catheter. Cardiac output measurement in critically ill patients is subject to many confounding factors such that, even under experimental conditions, the accuracy of bolus thermodilution may only be  $\pm 5\text{-}10\%$  (Nishikawa and Dohi 1993). Originally, blood oxygen content was measured directly using equipment such as the van Slyke or Scholander apparatus, but this demands considerable technical expertise and is time consuming. A more straightforward method of determining blood oxygen content became available with the development of integrated machines which measure haemoglobin concentration, oxygen tension, and haemoglobin oxygen saturation. With these primary measurements the oxygen content of blood could be calculated from the formula:

$$\text{Oxygen content} = ([\text{Hb}] \times \text{SO}_2 \times \text{Constant 1}) + (\text{pO}_2 \times \text{Constant 2})$$

Where: [Hb]	haemoglobin concentration
SO <sub>2</sub>	haemoglobin oxygen saturation
Constant 1	combining capacity of oxygen with haemoglobin
pO <sub>2</sub>	oxygen tension/partial pressure
Constant 2	solubility coefficient for oxygen in plasma

Constant 2, the solubility coefficient for oxygen in plasma, is a true physiological constant. Furthermore, the contribution of dissolved oxygen to the total oxygen content is relatively insignificant under normal physiological circumstances such that errors associated with oxygen tension measurement are unimportant. Constant 1, the combining capacity of haemoglobin with oxygen, is more problematic. Experimental studies suggest that when fully saturated 1g of pure haemoglobin can combine with 1.39mL of O<sub>2</sub>. This figure is widely quoted but has been disputed as being too high (Nunn 1996, Jolliet et al 1996). Blood normally contains small amounts of



haemoglobin derivatives such as carboxyhaemoglobin and methaemoglobin in quantities which vary according to exposure to environmental factors such as cigarette smoke. It is generally assumed that these haemoglobins take no part in active oxygen transport and that they effectively reduce the combining capacity for oxygen per unit of haemoglobin. As a result a combining capacity of 1.34mL is frequently used for calculations in vivo. Many modern cooximeters actually measure and quantify the proportions of haemoglobin subtypes in blood samples. However, there is no literature which examines which value for the combining capacity of haemoglobin is best for use in the critically ill even if true haemoglobin oxygen saturation is known.

In early studies, and in some contemporary work, haemoglobin oxygen saturation was calculated from blood gas variables rather than measured directly by cooximetry. Several formulae are available for this purpose all of which rely on assumptions regarding the shape and position of the oxygen dissociation curve (Gabel 1980). Recent work indicates that calculated oxygen saturation is subject to considerable error in comparison to cooximetry in critically ill patients, which introduces significant errors into the calculation of oxygen consumption by the reverse Fick method (Woda et al 1996). The errors associated with cooximeter measurement of saturation may also be significant, particularly for values on the steep part of the oxygen dissociation curve (Woda et al 1996, Beards et al 1994), and the accuracy of commercially available machines may differ significantly (Beards et al 1994).

The formula used almost universally for calculating  $\text{VO}_2$  in the critically ill since the early 1970s has thus been:

$$\text{VO}_2 = \text{Cardiac output} \times \{([\text{Hb} \times \text{SaO}_2 \times 1.34] + [\text{PaO}_2 \times 0.003]) - ([\text{Hb} \times \text{SvO}_2 \times 1.34] + [\text{PvO}_2 \times 0.003])\}$$

It is clear from the above discussion that errors associated with each measurement may be significant. Despite the enormous literature on oxygen kinetics in the critically ill, and the widespread use of these variables to guide therapy, there have been

virtually no studies examining the magnitude of errors in the final value for  $\text{VO}_2$  or the factors which influence the size of the errors in individual patients. Most published studies give no indication of the repeatability of the primary or derived measurements made and although these shortcomings are widely appreciated there is little work exploring the validity of the Fick method *in the clinical setting*.

## OXYGEN KINETICS

### Normal Physiology

Under normal resting conditions the global oxygen delivery ( $\text{DO}_2$ ) to tissues is the product of the cardiac output and the oxygen content of arterial blood:

$$\text{DO}_2 = \text{Cardiac output} \times ([\text{Hb} \times \text{SaO}_2 \times 1.34] + [\text{PaO}_2 \times 0.003])$$

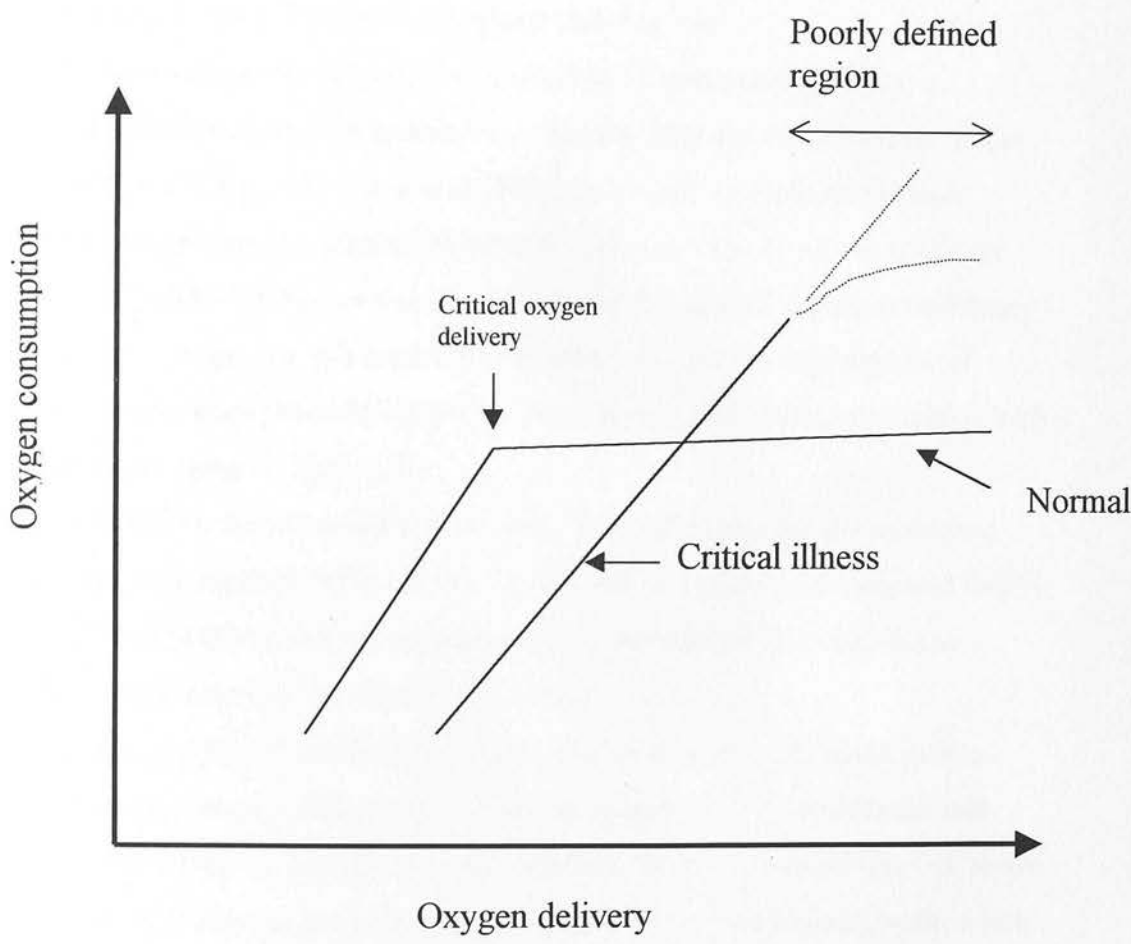
Oxygen consumption by tissues is determined by cellular requirements, primarily a function of metabolic rate. At rest the tissues extract approximately 30% of delivered oxygen (OER 0.3)(Leach and Treacher). Minor alterations in oxygen requirement by most tissues is accommodated by changes in oxygen extraction. If a significant increase in tissue oxygen requirement occurs there are two physiological responses. Firstly, tissue oxygen extraction may increase further; a global OER of up to 0.8 is possible in trained healthy individuals. This highest achievable extraction ratio is termed the critical OER (cOER) and has been determined in healthy humans from exercise studies (Leach and Treacher 1992). The OER of different tissues at rest and their cOER during increased demand varies widely such that global measurements do not reflect individual organs. The ability of tissues to increase their OER is probably a function of the improvement in *convective* transport to tissues (ie flow), and *diffusive* transport down a gradient for  $\text{pO}_2$ . The latter is determined by the  $\text{pO}_2$  itself and by the nutritive capillary density, control of which is extremely complex and incompletely understood. The second physiological response to increased oxygen demand is to increase global oxygen delivery via an increase in cardiac output. In health cardiac output can increase up to 5 times normal in response to increased demand (Leach and



Thus under normal physiological conditions the supply of oxygen to tissues occurs in response to altered demand, demand and supply are coupled, and the condition can be termed *physiological supply dependency*.

Further understanding of the relationship between oxygen delivery and consumption came from animal studies in which oxygen delivery was actively manipulated under conditions of constant demand and the effect on consumption determined. These indicate that if  $\text{DO}_2$  is augmented  $\text{VO}_2$  remains constant and the response of the tissues is to decrease the OER (Cain 1983). If oxygen delivery is decreased artificially there is initially no change in oxygen consumption until a critical level of  $\text{DO}_2$  is reached below which oxygen consumption falls progressively (Cain and Curtis 1991)(figure 1.1). Below this point, the critical  $\text{DO}_2$  ( $\text{cDO}_2$ ), oxygen consumption becomes truly supply *limited*, and anaerobic metabolism occurs in the tissues. The value of  $\text{cDO}_2$ , as with cOER, appears to be tissue and organ dependent during health. There are no studies in healthy humans which examine the effects of progressive reduction in  $\text{DO}_2$  on oxygen consumption since these would be unethical. From animal studies the classic two phase relationship has been demonstrated convincingly and indicate that, under laboratory conditions, the  $\text{cDO}_2$  varies from 6-10  $\text{mL.kg}^{-1}.\text{min}^{-1}$ , and the cOER from 0.5-0.8 (Leach and Treacher 1992). The only studies which have addressed this question in “healthy” humans examined anaesthetised patients undergoing cardiac surgery immediately prior to and immediately following cardiopulmonary bypass (Shibutani et al 1983; Komatsu et al 1987). Many data pairs for  $\text{DO}_2$  and  $\text{VO}_2$  (calculated by the Fick method) in many patients were pooled and plotted. From this a  $\text{cDO}_2$  of about  $330 \text{ mL.min}^{-1}.\text{m}^{-2}$  was obtained, below which the mean slope by linear regression analysis for the  $\text{DO}_2/\text{VO}_2$  relationship was 0.14, and above which the slope was zero (Shibutani et al 1983). The cOER associated with the  $\text{cDO}_2$  was only 0.30-0.35, significantly lower than in exercise studies or in animal studies (Komatsu et al 1987).

Figure 1.1: Classic description of the relation between oxygen delivery and oxygen consumption in health (assuming constant oxygen demand), and during critical illness.



## Oxygen Kinetics in the Critically Ill.

### *Oxygen consumption.*

Oxygen consumption is the primary determinant of metabolic rate, which is increased in most forms of critical illness. Many factors influence metabolic rate in the critically ill and are considered later in this introduction. An important consideration in studies of oxygen kinetics in the critically ill is that metabolic rate varies spontaneously and significantly in response to therapeutic and non-therapeutic events as diverse as physiotherapy and the presence of relatives (Weissman et al 1984,1991).

### *Relationship between Oxygen Delivery and Consumption.*

The frequent occurrence of metabolic acidosis and high circulating lactate concentrations in critically ill patients has led to the view that tissue hypoxia occurs frequently in these patients (Soni et al 1993). As a result, research efforts have focussed on defining the relationship between  $\text{DO}_2$  and  $\text{VO}_2$  during critical illness. The considerable literature in this area is confusing because of varying methodology, differing patient groups, and apparently contradictory findings. The majority of studies have indicated that the  $\text{DO}_2/\text{VO}_2$  relationship is altered in the critically ill with the following features (figure 1.1):

- 1) The  $\text{DO}_2/\text{VO}_2$  curve is shifted to the right. This implies that oxygen extraction capability is impaired at the tissue level. Clinical studies have demonstrated low OER in critically ill patients and an inability to increase OER in response to therapeutic interventions (Danek et al 1980).
- 2) The shape of the curve is different. Many studies suggest a curvilinear or linear relationship between  $\text{DO}_2$  and  $\text{VO}_2$  over the range of  $\text{DO}_2$  studied (Leach and Treacher 1992). In virtually all studies the range of  $\text{DO}_2$  examined was well above the normal  $\text{cDO}_2$  suggested by animal studies and the limited human work, which has led many to suggest that the  $\text{cDO}_2$  is considerably increased during critical illness. The dependence of  $\text{VO}_2$  on  $\text{DO}_2$  has been termed *pathological* supply dependency. This relationship has been demonstrated in animal models of sepsis (Nelson et al 1988, Cain and Curtis 1991). In man it was first reported in patients with ARDS (Powers et al 1973, Danek et al 1980), and subsequently in sepsis and

septic shock (Kaufman et al 1984, Astiz et al 1987, Bihari et al 1987). Perhaps surprisingly, others studies also reported pathological supply dependency in hypovolaemic shock (Kaufman et al 1984), congestive cardiac failure (Mohsenifar et al 1987), and chronic obstructive lung disease (Brent et al 1984).

In considering available studies it is useful to examine the possible confounding factors in oxygen kinetics studies in the critically ill:

1) *The direction of altering  $DO_2$* : The majority of studies have used therapeutic interventions which *increase*  $DO_2$  (Smithies and Bihari 1993). Many of these studies indicate an accompanying increase in  $VO_2$ , but none have demonstrated a plateau phase or a  $cDO_2$  at a higher level than observed in healthy humans and in animal studies. There are few studies which decreased  $DO_2$  as this is generally unethical. However, in patients with ARDS, moderate reductions in  $DO_2$  induced by PEEP did not reduce  $VO_2$  (Annat et al 1986, Carlile and Gray 1989). The most important study in this area, and the only which has identified the  $cDO_2$  and  $cOER$  in individual critically ill humans, studied critically ill humans during withdrawal of therapy after this decision had been made on clinical grounds (Ronco et al 1993). This group studied 9 septic and 9 non-septic patients during progressive reduction in  $DO_2$  and found the  $cDO_2$  was about  $4\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  and the  $cOER$  was about 0.6. There was also no difference between septic and non septic patients. This work suggested that  $cDO_2$  was *less* than the levels of  $DO_2$  usually present in critically ill patients, in direct contradiction to work in which  $DO_2$  was increased.

2) *The method of altering  $DO_2$* : A concern with the interpretation of many studies which increased  $DO_2$  has been that the inotropic agents used may themselves have increased metabolic rate such that linkage between  $DO_2$  and  $VO_2$  was physiological coupling rather than pathological supply dependency. The thermogenic effects of adrenaline, noradrenaline, dobutamine, and dopamine have been clearly demonstrated in healthy humans (Ruttiman et al 1991, Bhatt et al 1992, Green et al 1992, Ensinger et al 1993 and 1995), although during metabolic stress

thermogenesis attributable to inotropes may be blunted (Uusaro et al 1995). The relative importance of these effects in studies of oxygen kinetics in the critically ill remains controversial.

3) *Method of measuring  $VO_2$* : Until the 1990s the reverse Fick method was used almost universally in oxygen kinetics studies in the critically ill because it was cheap and feasible, whereas the technology for gas analysis was unavailable to most researchers. As discussed above few studies have addressed the accuracy of this method in the critically ill. A further potential confounding factor in these studies was mathematical coupling whereby an artificial relationship between  $DO_2$  and  $VO_2$  might occur because measurements of cardiac output and arterial oxygen content are used to calculate both variables of interest. This problem was considered by Archie (1982) but, despite widespread appreciation of the *potential* for mathematical coupling to explain the supply dependency observed in studies, few studies examined its importance *in practice* until after 1990. The only group to address the issue were Stratton and colleagues (1987) who applied a statistical solution which sought to correct for mathematical coupling to pooled retrospective data from several different studies. Their conclusion, that supply dependency still existed after the effect of mathematical coupling was removed, was widely quoted as justification for the continued use of the Fick method to determine  $VO_2$ .

Early automated gas exchange monitors were insufficiently accurate for use in ventilated patients, but technological developments resulted in several metabolic monitors becoming commercially available in the late 1980s. When these were used to measure  $VO_2$  independent from  $DO_2$  investigators found no evidence of supply dependency in resuscitated patients with sepsis or ARDS (Ronco et al 1991 and 1993, Hanique et al 1994a). Furthermore, these studies found that simultaneous calculations of  $VO_2$  with the reverse Fick method did indicate supply dependency implicating mathematical coupling as a major confounding factor. Finally, Phang and colleagues (1994) prospectively applied the statistical solution for mathematical coupling proposed by Stratton and colleagues to  $DO_2/VO_2$  data from

*individual* patients and found that, after correction, no supply dependency was present. It is now widely accepted that mathematical coupling is potentially important and that oxygen kinetics studies should use independent methods of determining  $\text{DO}_2$  and  $\text{VO}_2$  (Pinsky 1994).

- 4) *Volume status*: In many early studies patients were probably fluid deplete in comparison with current levels of fluid resuscitation. Under these conditions increasing  $\text{DO}_2$  may increase  $\text{VO}_2$  because some tissues, such as the splanchnic tissues, were below their  $\text{cDO}_2$ . These studies may have simply indicated inadequate volume resuscitation rather than pathological supply dependency (Smithies and Bihari 1993). In those recent studies which failed to demonstrate supply dependency volume resuscitation, as measured by the central venous and pulmonary artery occlusion pressures, was more aggressive prior to manipulating  $\text{DO}_2$ .
- 5) *Data numbers*: Many studies have used small numbers of data, often only two data pairs, to construct  $\text{DO}_2/\text{VO}_2$  curves, a feature which amplifies the effect of measurement error and mathematical coupling (Bartlett and Dechert 1990, Walsh and Lee 1998). In addition the range of  $\text{DO}_2$  examined has frequently been small. Few studies have constructed curves in individual patients with many data pairs over a wide range of  $\text{DO}_2$ .

There are very few studies in which all of these methodological problems are adequately considered (Russell and Phang 1994). Although a subject of continuing controversy most studies in which potentially confounding factors are eliminated or minimised conclude that pathological supply dependency either does not exist, or occurs far less frequently than suggested by earlier work (Russell and Phang 1994, Hanique et al 1994a)



### *Relationship between $DO_2$ , $VO_2$ , and outcome.*

The pioneering work of Schoemaker (1972) resulted in many studies which have examined the relationship between oxygen derived variables and outcome in various groups of critically ill patients. These can be divided broadly into three categories for consideration:

- 1) Studies which examine the association between oxygen derived variables and outcome
- 2) Studies in which oxygen delivery was increased by intervention, and the relationship between the resultant change in  $VO_2$  or OER and outcome examined.
- 3) Studies which examined the effect on outcome of targeting a particular level of  $DO_2$  or  $VO_2$  in all patients; so-called "goal-directed therapy".

*Association between oxygen derived variables and outcome:* In observational studies Schoemaker demonstrated that patients in whom cardiac output,  $DO_2$  and  $VO_2$  were elevated following surgery or during critical illness had higher survival rates than those with normal or decreased values (Schoemaker et al 1972, 1973, 1993). This association has been confirmed by others in patients with ARDS (Hankeln et al 1987, Russell et al 1990) and sepsis (Abraham et al 1984, Tuchs Schmidt et al 1989, Hayes et al 1993), as well as following major procedures such as liver transplantation (Nasraway et al 1995).

*Response to therapy aimed at increasing  $DO_2$ :* Several studies indicate that a failure to increase  $DO_2$  in response to therapeutic interventions aimed at achieving this predicts a poor outcome in comparison with patients in whom  $DO_2$  does increase (Hayes et al 1997, Vallet et al 1993, Yu et al 1995). In most studies an inability to increase  $VO_2$  in response to such interventions was also strongly associated with subsequent poor outcome (Hayes et al 1994, 1997; Vallet et al 1993) although one much quoted study had opposite findings (Bihari et al 1986).

*Goal-directed therapy:* As a result of the association between high levels of  $DO_2$ , cardiac output,  $VO_2$  and improved outcome many investigators have attempted

to test the hypothesis that increasing levels of these variables to predefined “supranormal” goals in all patients improves overall outcome. Studies of “goal oriented therapy” (usually cardiac index  $>4.5 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ,  $\text{DO}_2 >600 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ,  $\text{VO}_2 >170 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ) have been performed in high risk surgical patients (Schoemaker et al 1982, Schoemaker et al 1988, Boyd et al 1993, Ziegler et al 1997), trauma patients (Fleming et al 1992, Bishop et al 1995), septic patients (Edwards et al 1989, Tuchschiidt et al 1992) and heterogeneous groups of critically ill patients (Yu et al 1993, Hayes et al 1994, Gattinoni et al 1995). The results of these studies have been contradictory and interpretation complicated by methodological problems such as method of randomisation, level of fluid resuscitation, choice of inotrope, and post hoc analyses (Gasman et al 1996). A recent meta-analysis concluded that goal directed therapy conferred no benefit in patients with established critical illness but may be of value in those undergoing high risk surgery (Heyland et al 1996, Hinds and Watson 1995).

#### ENERGY METABOLISM IN CRITICAL ILLNESS

The metabolic response to injury and sepsis is extremely complex. In general terms it is characterised by an increase in resting energy expenditure, increased catabolism of protein and fat, negative nitrogen balance, hyperglycaemia, and increased hepatic glucose production (Chiolero et al, 1997). As a result of these processes there is a progressive reduction in body cell mass. These processes occur as part of a systemic inflammatory response which appears to be a non-specific stereotyped response to injury which is caused by the activation of a complex system of mediators. This stress response is thought to promote elimination of infection and facilitate healing and recovery. It is currently hypothesised that, under poorly understood circumstances, the stress response can itself become harmful to an organism by causing organ damage and ultimately multiple organ failure (Barton and Cerra 1989). Understanding the balance between the beneficial and detrimental effects of the inflammatory response, and how they are modulated, has been a focus of intense research in the critically ill but is not yet fully understood (Bone 1996). The known mediators which



control the inflammatory response include cytokines, oxygen derived free radicals, prostanoids, leukotrienes, and endothelins (Blackwell and Christman 1996). Release of these mediators occurs in association with activation of white blood cells which is an energy consuming process (Nunn 1996). Inflammatory mediators have the potential to induce alterations in metabolism in virtually all tissues which have been studied. These alterations include changes in the pattern and rate of synthesis of biological molecules which increases energy requirement by cells. In the liver the stress response induces changes in hepatic protein synthesis which include increased synthesis of the “positive” acute phase proteins, including C Reactive Protein (CRP), serum amyloid A,  $\alpha$ 1-acid glycoprotein,  $\alpha$ 1-antichymotrypsin and haptoglobin, and decreased synthesis of normal export proteins, notably albumin and transferrin (Wigmore et al 1998). Increases in circulating concentrations of the classic counter-regulatory hormones, namely adrenaline, noradrenaline, cortisol, and glucagon, induce protein breakdown, lipolysis, glycogenolysis, and gluconeogenesis. There is also evidence of increased resynthesis of proteins and lipids consistent with a generalised increase in the cycling of biochemical pathways (Burzstein et al 1989). These processes are all energy consuming.

### **Components of Energy Expenditure**

In healthy adults the *Total Energy Expenditure* (TEE) is usually considered to have 3 main components: basal metabolic rate (BMR), thermogenesis, and physical work.

*Basal metabolic rate* is defined as the energy expenditure of an individual at least 10 hours after previous nutritional intake, resting in a lying position, awake, and at normal body and ambient temperature, and without physical or psychological stress (Burzstein et al 1989). It is determined primarily by the Lean Body Mass. BMR maintains basic metabolic functions and represents approximately 60-70% of TEE in sedentary individuals (Chiolero et al 1997). Only 10-20% of BMR is devoted to mechanical work, primarily cardiac contraction and the work of breathing. The remaining 80-90% corresponds to the energy cost of biochemical pathways and cycles, and the function of membrane ion pumps.

*Thermogenesis* accounts for about 10% of TEE in healthy individuals. This proportion may change dramatically in response to altered ambient temperature. A decrease in ambient temperature results in an increase in energy expenditure due either to shivering or by activation of metabolic reactions releasing heat via hydrolysis of ATP. Shivering may increase energy expenditure by up to 300% (MacIntyre et al 1987). If ambient temperature rises energy expenditure will initially decrease, reaching a minimum in healthy individuals at about 27°C. Above this temperature energy expenditure again rises because sweating and other heat-losing processes are energy consuming. The ambient temperature within which energy expenditure is at a minimum is termed the “zone of thermal neutrality” and is 27-29°C in healthy men (Burzstein et al 1989). Injury increases this temperature (for example in burned patients it is typically 32°C), and the response may also be influenced by the administration of anaesthetic drugs (Sessler 1997).

The other thermogenic component of energy expenditure is food. Energy expenditure increases in response to feeding irrespective of the route of administration. The factors which account for this *diet* or *substrate induced thermogenesis* are incompletely understood but are probably the energy associated with absorption, handling, and storage, and also a nutrient-induced activation of the sympathetic nervous system (facultative thermogenesis)(Chiolero et al 1997). The proportion of the energy content of nutrients devoted to thermogenic processes amounts to about 20-30% for proteins, 5-10% for carbohydrates and less than 5% for fats, unless nutrients are given in excess when thermogenesis can be considerably greater.

*Physical work* represents 20-30% of TEE in healthy individuals but is highly dependent on the level of physical activity.

*Resting energy expenditure* (REE) is a term often used to describe BMR plus diet-induced thermogenesis.

## Determinants of energy expenditure during illness

*Stage of Illness:* Classic studies of the metabolic response to injury describe 2 phases: the initial *ebb* phase followed by the *flow* phase (Cuthbertson 1942, Moore 1953). Each phase varies in duration and severity in proportion to the extent and nature of the injury. The ebb phase is characterised by hypovolaemia, hypotension, hypothermia, and increased sympathetic activity, but energy expenditure is actually decreased. In modern terminology this period represents hypovolaemic shock, or the pre fluid resuscitation state during which oxygen consumption and energy metabolism is limited by oxygen supply to the tissues. With contemporary resuscitation techniques this period should be shortlived. The flow phase is characterised by hypermetabolism and increased energy expenditure, and is equivalent to the classic stress response. In clinically resuscitated critically ill patients energy expenditure may change dramatically during the course of their illness. For example, Kreyman et al (1993) found energy expenditure was approximately 160% of reference values in patients with sepsis (clinical signs of infection but no organ failure), and in those recovering from septic shock, but was significantly lower (about 120%) in patients with sepsis syndrome (sepsis plus organ failure), and lowest of all (about 100%) in patients with septic shock (sepsis syndrome with hypotension requiring vasopressors).

*Age and Sex:* As described above the principal determinant of BMR is lean body or fat free mass. Lean body mass decreases with increasing age, which accounts for the decreases in BMR and REE which are features of increasing age. The pattern of the metabolic response to injury is, however, similar irrespective of age (Watters et al 1989, Chioloro et al 1997). Energy expenditure is lower in females than males of similar size because the former have a lower lean body mass.

*Temperature:* Fever is an energy-consuming process which is associated with a 10-15% increase in energy expenditure for each degree Celsius elevation of temperature (Chioloro et al 1997). The effect of cooling on energy expenditure is complex and, as described above, depends on the level of activation of temperature conserving and generating processes. Manthous and colleagues (1995a) found that during cooling of

febrile critically ill patients, oxygen consumption decreased by approximately 10% per degree Celsius, which corresponds to similar changes in energy expenditure.

*Treatments:* Catecholamines used for haemodynamic support activate metabolism. This is true for all commonly used agents but is maximal for the naturally occurring adrenergic agents adrenaline, noradrenaline, and dopamine, and less marked with synthetic agents such as dobutamine (Chiolero et al 1997). In healthy individuals adrenaline, noradrenaline, dobutamine, and dopamine all have dose-dependent effects on metabolic rate (Ensinger et al 1993, 1995, Bhatt et al 1992, Ruttiman et al 1991, Green et al 1992). However, these thermogenic effects may be attenuated in the presence of an established stress response (Uusaro et al 1995), and assessment of the thermogenic response to catecholamines in individual critically ill patients is difficult.

Mechanical ventilation reduces the work of breathing which may be considerable in critically ill patients, particularly those with respiratory failure (Viale et al 1988, Shikora et al 1990, Manthous et al 1995b). Sedative and analgesic drugs, and neuromuscular paralysis all decrease energy expenditure by reducing anxiety, pain, and muscular activity (Chiolero et al 1997).

*Diet-induced thermogenesis:* The effect of diet on energy expenditure was considered earlier. In healthy individuals the thermic effect of food is dependent on the nature of the substrates ingested and is directly proportional to the amount of calories ingested (D'Alessio et al 1988). In hypermetabolic critically ill patients diet-induced thermogenesis may be blunted, and the close relationship with the nature of the substrate blurred (Chiolero et al 1997). In view of the unpredictable effects of feeding on energy expenditure most studies of energy expenditure are carried out in the fasting state.

### **Prediction of Energy Expenditure**

In normal healthy subjects REE can be predicted with reasonable accuracy from body weight, height, age and sex. Numerous predictive formulae are described for this

purpose, of which the best known is the Harris-Benedict equation (Harris and Benedict 1919).

Harris Benedict equations: Wt=weight in kg, Ht=height in cm.

Men REE (kJ) =  $278 + 57.5Wt + 20.93Ht - 28.35age$

Women REE (kJ) =  $2741 + 40.0Wt + 7.74Ht - 19.56age$

Although widely used, predictive equations have been shown to be unreliable in malnourished patients (Roza and Shizgal 1984), and have a low predictive value in critically ill patients (Weissman et al 1986, Makk et al 1990, Weissman and Kemper 1992).

### ACUTE LIVER FAILURE

Acute liver failure is an umbrella term which encompasses various clinical presentations resulting from acute loss of hepatic function of varying aetiology.

*Fulminant hepatic failure* is the term traditionally used to define sudden onset of liver failure accompanied by hepatic encephalopathy developing within 8 weeks of the onset of illness, in the absence of previous liver disease (Trey and Davidson 1970).

Definition of fulminant hepatic failure and its subtypes is a subject of debate internationally which is influenced by local aetiology and diagnostic practice (Gimson 1996). The most recent UK terminology suggests the term *hyperacute liver failure* for patients developing encephalopathy within 7 days of jaundice, *subacute liver failure* when it develops within 8-28 days of jaundice, and *subacute liver failure* when it develops between 29-72 days of jaundice. The aetiology, clinical course, and prognosis differ between these clinical syndromes. A high incidence of cerebral oedema but relatively good prognosis are associated with hyperacute liver failure; conversely prognosis is poor with medical management alone in patients in whom the delay between jaundice and encephalopathy is prolonged >7days.

## Aetiology

The aetiology of fulminant hepatic failure is summarised in table 1(1).

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TABLE 1(1): Aetiology of acute liver failure.

CAUSE	AGENTS/PATHOGENESIS
Viral Hepatitis	Hepatitis A, B, C, D, E Herpes Simplex Virus
Drugs	Paracetamol Halothane Miscellaneous idiosyncratic reactions
Toxins	<i>Amanita Phalloides</i> Carbon tetrachloride
Vascular	Ischaemia Venoocclusive disease (including Budd-Chiari syndrome) Heatstroke
Malignant Infiltration	
Miscellaneous	Wilson's Disease Acute Fatty Liver of Pregnancy Reye's Syndrome

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Paracetamol hepatotoxicity is the commonest cause in the UK usually after ingestion of more than  $150\text{mg.kg}^{-1}$ . Lower doses may prove hepatotoxic in patients with enzyme induction due to alcohol abuse or the use of enzyme inducing drugs which result in induction of the cytochrome system (eg anticonvulsants or isoniazid)(Vale and Proudfoot 1995). Ingestion of multiple lower "therapeutic" doses of paracetamol



over several days can also result in severe hepatic damage. Paracetamol hepatotoxicity can be prevented by the administration of N-acetylcysteine which is considered later in this introduction. In most other countries viral hepatitis is the most common aetiology, although fulminant hepatic failure complicates <1% cases of viral hepatitis overall (Gimson 1996). The factors which cause progression to liver failure are incompletely understood but probably include host factors, primarily immunological, viral inoculum, and strain of virus (Gimson 1996).

**Clinical Features and Management**

*Hepatic Encephalopathy and Cerebral Oedema*

The severity of encephalopathy in fulminant hepatic failure is generally graded clinically (table 1.2).

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TABLE 1.2: Clinical grading of hepatic encephalopathy.

GRADE 1	Mild confusion, poor concentration, dysphoria, sleep pattern reversal. Fully coherent when roused
GRADE 2	Increasing confusion and disorientation but still rousable and able to be rational.
GRADE 3	Sleeping most of the time, but rousable to command. May be markedly agitated and aggressive.
GRADE 4	Not rousable to command. Variable response to pain. Hyperventilation, pupillary abnormalities, extensor plantars, and opisthotonus may all occur but correlate poorly with the presence of raised intracranial pressure.

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Most patients with grade 4 encephalopathy require tracheal intubation for airway protection. The pathogenesis of hepatic encephalopathy in acute liver failure is unclear (Gimson 1996). Neurotoxicity secondary to ammonia accumulation is traditionally

implicated although recent evidence implicates  $\gamma$ -aminobutyric acid (GABA) pathways as a major cause of neuronal depression although pharmacological reversal with benzodiazepine antagonists only improves coma temporarily (Mullen et al 1988). Serotonergic, dopaminergic, and glutaminergic pathways may also be important (Ferenci 1994).

Cerebral oedema accounts for up to 50% of deaths from fulminant hepatic failure. It is associated with intracranial hypertension and occurs in 70-80% of patients with grade 4 encephalopathy (Gimson 1996). The aetiology of cerebral oedema is unclear. Brain water is increased in this condition probably as a result of both directly cytotoxic and vasogenic (blood-brain barrier leakage) mechanisms (Blei 1991). Inhibition of brain  $\text{Na}^+/\text{K}^+$  ATPase, altered permeability, glutamine accumulation, and direct astrocyte toxicity have all been proposed but are unproven. The relationship between intracranial hypertension and radiological evidence of oedema is poor (Munoz et al 1991), and oedema alone is unlikely to explain the precipitous changes in intracranial pressure which can accompany this condition (Lidofsky et al 1992). These may result from acute alterations in cerebral blood flow or cerebral blood volume. Contradictory data exist concerning cerebral blood flow in patients with fulminant hepatic failure; most data indicate that it is decreased in the majority of patients, but it may be increased in some patients with severe encephalopathy, possibly in association with altered autoregulation (Ferenci 1994).

Clinical signs of cerebral oedema and intracranial hypertension are unreliable in patients with hepatic encephalopathy and accurate detection relies on the use of direct intracranial pressure monitoring (Gimson 1996), although no prospective study has been performed to evaluate the safety and efficacy of this potentially hazardous procedure. The use of mannitol in severe fulminant hepatic failure is associated with improved survival, but steroids and hyperventilation are of no value (Canalese et al 1982, Ede et al 1986). There is evidence that mannitol and N-acetylcysteine increase cerebral blood flow in patients with fulminant hepatic failure (Wendon et al 1994). It is unclear if cerebral autoregulation is deranged in humans with fulminant hepatic



failure, but the response to acute hypocapnia appears to be preserved (Wendon et al 1994).

### *Cardiovascular and Pulmonary Disturbance*

Profound haemodynamic changes occur in fulminant hepatic failure. Characteristically peripheral vasodilatation occurs in association with an increase in cardiac output. Hypotension occurs in approximately 50% of patients with grade 4 encephalopathy and is associated with a poor prognosis (Gimson 1996). As a result of high cardiac output,  $DO_2$  is generally high, and is further increased by vasodilators such as prostacyclin (Harrison et al 1991). Oxygen extraction ratio is frequently extremely low and plasma lactate concentrations elevated, which led Bihari and colleagues (1985) to hypothesise that tissue hypoxia was present in these patients. Studies which manipulated oxygen delivery in patients with fulminant hepatic failure are considered later in this introduction.

Pulmonary vascular resistance is low in most patients. Significant acute lung injury occurs in up to 30% of cases of paracetamol hepatotoxicity, particularly when acute renal failure coexists, and is associated with poor outcome (Baudouin et al 1995). Pneumonia and gastric aspiration also occur frequently.

### *Renal and Metabolic Dysfunction*

Acute renal failure complicates about 50% of cases and is a strong predictor of adverse outcome (Lee 1994). The aetiology is multifactorial and includes hypovolaemia, direct tubular toxicity (in the case of paracetamol), and functional renal failure (the hepatorenal syndrome). Electrolyte abnormalities are almost universal and include hyponatraemia, hypokalaemia, and hypophosphataemia (Gimson 1996). Alkalosis occurs more frequently than acidosis and may be respiratory (hyperventilation associated with encephalopathy) or metabolic (impaired hepatic urea synthesis) (Hawker 1993). Metabolic acidosis, when present, is associated with a poor prognosis. Hypoglycaemia occurs frequently due to impaired hepatic gluconeogenesis, and possibly hyperinsulinaemia resulting from reduced insulin clearance (Lee 1994).

Renal replacement therapy in fulminant hepatic failure is problematic. Intermittent haemodialysis is associated with significant morbidity because of hypotension and exacerbation of intracranial hypertension. Continuous modes of therapy cause less haemodynamic disturbance and greater neurological stability (Davenport et al 1993a, 1993b). The use of lactate based replacement solutions during high volume haemofiltration, in a condition characterised by hyperlactataemia, has been associated with worsening acidosis although there are no published studies using bicarbonate based solutions (Davenport et al 1990).

### *Coagulopathy*

Reduced synthesis of coagulation factors results in prolongation of the prothrombin and activated partial thromboplastin times. Only plasma levels of factor VIII are maintained. The prothrombin time and factor V concentrations have been shown to correlate closely with outcome and are widely used prognostically. Coagulopathy may be worsened by intravascular coagulation although disseminated intravascular coagulation and fibrinolysis are rarely severe clinically (Gimson 1996).

### *Sepsis*

Cell-mediated and humoral immunity are both compromised in fulminant hepatic failure. Bacterial sepsis occurs in approximately 80% of patients, most frequently with gram positive organisms (Rolando et al 1990). Fungal infection occurs in about 30% of patients and is associated with the use of antibiotics and coexistence of renal failure and leucopaenia.

### **Prognosis**

Despite intensive research into specific therapies such as charcoal haemoperfusion, steroids, prostaglandins, and glucagon no treatment other than supportive intensive care and liver transplantation have been widely proven to improve survival from fulminant hepatic failure (Lee 1994). As a result efforts have centred on defining criteria which predict death with sufficient sensitivity and specificity to guide the need

for liver transplantation. Two systems are currently widely used although neither is universally accepted, a fact which probably reflects different patterns of disease world wide. The King's College criteria, defined from a multivariate analysis of 588 patients managed over the 1973-1985 period, distinguish paracetamol from non-paracetamol aetiology and is used in the UK (table 1.3)(O'Grady et al 1989). Factor V concentrations and age (the Clichy criteria) are widely used in mainland Europe where paracetamol-induced liver failure occurs rarely (Bernuau et al 1986).

TABLE 1.3: Prognostic criteria used to guide liver transplantation in patients with fulminant hepatic failure.

KING'S CRITERIA	<p><b>Paracetamol overdose</b></p> <p>Arterial pH &lt; 7.30</p> <p><i>or all of the following:</i></p> <p>Prothrombin time &gt; 100 seconds</p> <p>Creatinine &gt; 300µmol.L<sup>-1</sup></p> <p>Grade 3 or 4 encephalopathy</p> <p>Prothrombin time increasing on day 4</p> <p><b>Non-paracetamol overdose</b></p> <p><i>Any three (irrespective of grade of encephalopathy) of:</i></p> <p>Aetiology non-A-non-B hepatitis, halothane or drug reaction</p> <p>Age &lt;10 or &gt;40 years</p> <p>&gt;7 days between onset jaundice and onset encephalopathy</p> <p>Serum bilirubin &gt; 300µmol.L<sup>-1</sup></p> <p>Prothrombin time &gt; 50 seconds</p> <p><i>or</i> Prothrombin time &gt; 100 seconds irrespective of grade of encephalopathy</p>
CLICHY CRITERIA	<p><i>Both of:</i></p> <p>Coma or confusion</p> <p>Factor V &lt; 20% (age &lt; 30 years) or &lt; 30% (age &gt; 30 years)</p>

## **N-Acetylcysteine in Fulminant Hepatic Failure**

N-acetylcysteine has proven benefit for treating paracetamol poisoning if given within 15 hours of ingestion (Vale and Proudfoot 1995). Harrison et al (1990) reported a retrospective survey of patients presenting with fulminant hepatic failure to King's College Hospital who received N-acetylcysteine between 10 and 36 hours after paracetamol ingestion. They documented an improved outcome in patients who had first received the drug during this period in comparison with those who had not, despite no measurable effect on hepatic function as judged by the prothrombin time. The same group subsequently reported a small prospective randomised trial of 50 patients with paracetamol-induced fulminant hepatic failure who had not previously received N-acetylcysteine (Keays et al 1991). After admission to the liver unit patients were randomised to receive either N-acetylcysteine, using a standard infusion rate which continued until recovery or death, plus "conventional intensive liver care", or conventional intensive liver care alone. In these patients the mean time elapsed from paracetamol ingestion to N-acetylcysteine administration was 55 hours, significantly longer than reported in any other study. There was a statistically significant difference in mortality between the groups with a 28% reduction in the N-acetylcysteine-treated group, representing a difference of 7 deaths between the two groups of 25 patients. Patients in the N-acetylcysteine group developed fewer clinical signs of cerebral oedema (intracranial pressure was not measured) and had reduced requirements for inotropic drug support. The incidence of acute renal failure was 20% less (a difference of 5 patients) in the N-acetylcysteine group although this was not statistically significant. As with the earlier uncontrolled study there was no difference in prothrombin time, considered the best measure of liver function, between the groups at any time.

This study was provocative but critical appraisal raises several important issues. Firstly, the study was not blinded introducing the potential for bias particularly when "soft" data such as "clinical evidence of cerebral oedema" was collected. Secondly, there is little available data concerning the conduct of "conventional intensive care", such as protocols for fluid resuscitation, antibiotic therapy, or nutrition. Thirdly, there

is no data regarding the incidence of infection which is the second most common cause of death after cerebral oedema (Lee 1994). Finally, complications known to be strongly associated with adverse outcome in fulminant hepatic failure, namely cerebral oedema, cardiovascular collapse, and acute renal failure, occurred more frequently in the control group. The authors hypothesised that these differences were explained by a therapeutic effect of N-acetylcysteine, but in a study of this size it was unclear whether differences in the incidence of these complications could have occurred by chance and accounted for the difference in mortality observed. Of particular relevance was the management of acute renal failure which occurred in 50% of the patients. This was managed using either intermittent haemodialysis or continuous arteriovenous haemofiltration but it was not stated which patients received which treatment and whether differences existed between the groups. As noted above serious complications occur more frequently when intermittent haemodialysis is used in comparison with continuous arteriovenous haemofiltration (Davenport et al 1993a, Davenport et al 1993b).

The mechanism of the proposed beneficial effect of N-acetylcysteine in these studies was unclear. It was unlikely that the drug significantly altered liver function as laboratory measures of hepatic function were no different from untreated patients. The King's group proposed an alternative mechanism of action based on other work from their centre. In an uncontrolled study Harrison et al (1991) examined the short term effect of the same dosage regimen for N-acetylcysteine on oxygen delivery, haemodynamic state, and oxygen consumption in 12 patients with paracetamol-induced fulminant hepatic failure and 8 patients with acute liver failure from other causes. Measurements of cardiac output, pulmonary artery pressures, and pulmonary capillary wedge pressure were made using a pulmonary artery catheter. Oxygen delivery, oxygen consumption, and oxygen extraction were calculated using standard formulae. Measurements were made at a baseline time point and then on one occasion 30 minutes after starting the N-acetylcysteine infusion. With the protocol used the authors also studied the effects of prostacyclin infusion alone and in combination with N-acetylcysteine. The principal findings of this study were that 30 minutes after



starting the N-acetylcysteine infusion significant increases in cardiac output, oxygen delivery, mean arterial pressure, left ventricular stroke volume, left ventricular stroke work, oxygen consumption, and oxygen extraction ratio occurred, accompanied by a decrease in systemic vascular resistance. These changes were most pronounced in the patients with paracetamol-induced fulminant hepatic failure in whom a 46% increase in oxygen consumption was described, but were also observed in the non-paracetamol group. These findings were equally provocative to those of the outcome study. In a group of critically ill patients N-acetylcysteine appeared to improve cardiac function, peripheral perfusion, and oxygen delivery and extraction consistent with the amelioration of tissue hypoxia. These observations were made at a time when intense research interest was focused on pathological supply dependency and tissue hypoxia in the critically ill. Many agents had been utilised which increase oxygen delivery to tissues but none had consistently been shown to improve oxygen extraction. Another study from the King's College group, using similar methodology, had suggested that adrenaline and noradrenaline might worsen oxygen extraction and consumption despite improving blood pressure (Wendon et al 1992). As low oxygen delivery, consumption and extraction were clearly associated with poor outcome, the discovery of an agent which might improve all of these variables was of major significance. The authors hypothesised that this might account for the reduction in mortality attributed to the late administration of N-acetylcysteine in patients with fulminant hepatic failure. They also hypothesised that the ability of N-acetylcysteine to replenish tissue sulphydryl groups might improve microvascular blood flow by increasing production of nitric oxide.

Critical appraisal of this study raises several important issues. Firstly, the results may have been affected by mathematical coupling because the reverse Fick method was used to calculate oxygen consumption. Secondly, only two data points were collected, before and after starting N-acetylcysteine, yet no estimation of the measurement errors present was made. Thirdly, none of the patients studied required inotropic support and median plasma lactate concentration at  $2.5 \text{ mmol.l}^{-1}$  was only marginally elevated suggesting that some patients despite being studied 33 to 96 hours after

paracetamol overdose did not have severe liver failure. Finally, patients were only studied 30 minutes after starting N-acetylcysteine. With the dosage regimen used a very large loading dose is administered over 15 minutes which results in high plasma concentrations of the drug which subsequently decline rapidly (Prescott et al 1989). It was unclear from the study whether the effects observed were related to plasma concentrations or if they were sustained during the subsequent infusion.

These studies have never been repeated but their conclusions are widely cited in the hepatology and critical care literature. N-acetylcysteine has become a standard treatment for fulminant hepatic failure in many centres worldwide.

## **LIVER TRANSPLANTATION**

The anaesthetic and surgical management of liver transplantation involves an understanding of the complex cardiopulmonary, metabolic, and haematological changes which occur at different stages of the procedure in patients with deranged physiology as a result of acute or chronic liver disease. The procedure is usually considered in three phases: the preanhepatic, anhepatic, and postanhepatic.

### **The preanhepatic phase.**

During this stage the liver is mobilised through a bilateral subcostal incision. The onset of the anhepatic phase occurs with the occlusion of the recipient portal vein followed by occlusion of the hepatic veins or perihepatic inferior vena cava after which the recipient liver is removed. Most patients undergoing liver transplantation have a high cardiac output and low vascular resistance as is typical in acute and chronic liver disease. Patients are generally haemodynamically stable during the preanhepatic period although the sudden drainage of massive ascites can be associated with rapid fluid shifts (Carton et al 1994).



## **The anhepatic phase.**

The anhepatic phase lasts from clamping the recipient portal vein until vascular reperfusion of the donor liver. A number of specific problems are associated with this period:

*Haemodynamic instability:* When the inferior vena cava is clamped above and below the liver, and the portal vein occluded, venous return to the heart is acutely decreased. This results in arterial hypotension and a decrease in cardiac output (Estrin et al 1989, Carton et al 1994, Kang et al 1989). In addition, infrahepatic venous pressures increase such that the perfusion pressure to organs such as the gut and kidneys may be reduced, and venous blood loss increased (Merritt et al 1990). Partial reversal of these changes can be achieved by fluid loading, although excessive administration may be complicated by fluid overload when the clamps are removed at reperfusion. Clamping of major vessels alone was the original surgical technique described for liver transplantation and it is still used in many centres either universally or in selected patients. However, two techniques have been devised which seek to maintain venous return to the heart during the anhepatic phase.

### **1) Venovenous bypass.**

There are many variations on this technique but the principle is to divert blood via an extracorporeal circuit from the inferior vena cava (usually from the femoral vein) and portal vein to the subclavian or internal jugular veins. Flow is usually generated with a centrifugal pump system with maximum achieved flow rates typically of 2-3 L.min<sup>-1</sup>. Anticoagulation is rarely used. The proposed benefits of venovenous bypass are greater haemodynamic stability, reduced blood product requirement, improved perioperative renal function, and reduced metabolic disturbance (Carton et al 1994). Complications include hypothermia, air embolism, thromboembolism, neurovascular complications of cannulation, and the requirement for trained operators.

## 2) Piggyback technique.

With this technique venous return to the heart is maintained without the need for extracorporeal circulation. Instead of cross clamping the inferior vena cava above and below the recipient liver and anastomosing the donor liver with donor vena cava *en bloc*, the recipient liver is carefully dissected from around the vena cava and the hepatic veins identified and dissected high up into the liver parenchyma. A side-biting clamp is then applied across the hepatic veins and part of the inferior vena cava such that vena caval flow to the heart continues. The hepatic veins are then divided and the recipient liver removed. For anastomosis of the donor liver the recipient hepatic veins are fashioned into a single vessel and the donor superior vena cava piggybacked on to the recipient vena cava (Tzakis et al 1989). During the anhepatic period the portal vein can either remain clamped or be drained into the inferior vena cava via a temporary portacaval shunt (Tzakis et al 1993). The advantages claimed for this approach include greater haemodynamic stability, improved renal and splanchnic perfusion, reduced cost, and greater post reperfusion stability (Figueras et al 1993, Belghiti et al 1995, Steib et al 1997, Howard 1997). However, it demands greater surgical skill and dissection, particularly if the recipient liver is closely applied to the vena cava.

There are no prospective randomised studies which compare these surgical techniques although a large number of anecdotal reports and small unrandomised studies have been published, reflecting the strong influence of personal preference on surgical practice in this area. These have conflicting results and there is a need for well-designed detailed studies examining both the physiological changes which occur with these different approaches and their relevance to morbidity and mortality.

*Coagulopathy:* Coagulopathy during liver transplantation is of multifactorial aetiology but requires careful correction in order to minimise blood loss. Preoperative liver disease results in variable reduction in coagulation factor production and abnormal platelet function. Intraoperative coagulopathy may worsen because of dilution, massive blood loss, hypothermia, and calcium chelation by citrate from blood

products (Carton et al 1994). Fibrinolysis can occur, typically at the time of reperfusion. Management of coagulopathy requires close monitoring with coagulation tests and the appropriate use of clotting factors. Aprotinin is widely used as prophylaxis against fibrinolysis and is associated with reduced transfusion requirements (Grosse et al 1993, Segal et al 1994).

*Metabolic Changes:* Progressive metabolic acidosis is classically described during the anhepatic phase as a result of tissue hypoperfusion, hypothermia, blood transfusion, and sometimes renal dysfunction. Acidosis is frequently accompanied by hyperlactataemia (Steib et al 1992). Although hypoglycaemia may complicate acute and chronic liver failure it occurs rarely during transplantation and hyperglycaemia occurs more frequently (Carton et al 1994). Various electrolyte abnormalities may occur during the anhepatic period the most important and frequent of which is ionic hypocalcaemia resulting primarily from citrate binding and hypothermia.

### **Reperfusion and the post anhepatic period.**

Reperfusion of the donor graft is the time associated with greatest clinical instability and most complications. Typically the rapid increase in venous return results in increased central venous pressure and an increase in cardiac output. This is associated with a variable increase in pulmonary artery pressures but systemic hypotension and vasodilatation (Webster et al 1994). The term “postreperfusion syndrome” describes severe forms of this haemodynamic pattern in which a decrease in mean arterial pressure of >30% occurs for at least 1 minute within 5 minutes of reperfusion (Aggarwal et al 1987). Other changes include cardiac dysrhythmias, heart block, and cardiac arrest. Hypothermia is also most severe at this time point because the graft, which is preserved in crushed ice, rapidly absorbs heat from the recipient’s blood. These changes arise when surgical complications such as massive haemorrhage and air or thrombotic embolism may occur. The aetiology of post-reperfusion syndrome is unclear. Cardiac function appears to be well preserved although acute decreases in coronary perfusion pressure may occur and left and right ventricular dysfunction are described (De Wolf et al 1993, Carton et al 1994). Substances released from the graft

itself, or from tissues which were ischaemic during the anhepatic period, have been implicated (Goode et al 1994, Bellamy et al 1997). Rapid metabolic changes may contribute including hyperkalaemia, hyperglycaemia, hypocalcaemia, hyperlactataemia and worsening acidosis. Management of reperfusion involves correcting metabolic abnormalities during the anhepatic phase, and the careful use of fluids and inotropes (Carton et al 1994). Patients with fulminant hepatic failure are particularly at risk at the time of reperfusion because of cardiovascular instability and intracranial hypertension which often worsens at this time point and can result in cerebellar coning (Carton et al 1994). The factors which cause these complications and the best means of preventing them are poorly understood.

Following reperfusion surgery involves securing haemostasis, completing vascular anastomoses, and anastomosing the bile duct. During this period the production of bile, and improvements in acidosis and hyperlactataemia are evidence of graft function. Patients with fulminant hepatic failure often demonstrate a rapid improvement in neurological status. Post-operative monitoring in an intensive care unit is usual until consciousness is regained and tracheal extubation is performed. During this period close monitoring of biochemical and haematological parameters, together with clinical variables such as urine output are advisable.

### THE DELTATRAC METABOLIC MONITOR

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#### INTRODUCTION

For the studies which form the basis of this thesis gas exchange measurements were performed with the Deltatrac metabolic monitor (Datex, Helsinki, Finland). This device is designed primarily to determine oxygen consumption and carbon dioxide elimination in both spontaneously breathing and mechanically ventilated patients. From these measurements secondary variables including energy expenditure and respiratory quotient can be calculated. The Deltatrac system was designed to avoid the need for accurate measurement of gas volumes which has proved most problematic in the development of automated systems for measuring gas exchange. This is done by a flow dilution system using an accurate fixed flow generator in an open system of measurement. The problem of rapid and accurate measurement of gas fractions has been solved using infrared CO<sub>2</sub> analysers and paramagnetic oxygen analysers. The system has been validated under clinical conditions and in lung models by several independent groups.

#### MODE OF ACTION

##### *Spontaneous Ventilation*

A canopy is used to surround the subjects head and inspired gas is sucked through the canopy at a known, constant rate of about 40L.min<sup>-1</sup> (figure 2.1). The difference between inspired and expired oxygen fractions is measured with a rapid response, paramagnetic differential oxygen analyser (OM-101, Datex, Helsinki). The response time of this analyser is 130msec and the resolution 0.01%; responses are linear over the measurement range with negligible non-linearity error. The expired CO<sub>2</sub> fraction is measured with an infrared CO<sub>2</sub> analyser (CX-104, Datex, Helsinki). The resolution of this analyser is 0.01%, and its linearity is checked and corrected within the monitor by computer program. The system relies on the accuracy of the constant flow generator

which is constructed from a centrifugal fan. The construction of the fan enables it to generate a flow of  $700\text{L}\cdot\text{min}^{-1}$ , but a flow restrictor at the outlet of the fan decreases the flow down to  $45\text{L}\cdot\text{min}^{-1}$  which makes it insensitive to pressure fluctuations upstream. Compensation is made for ambient pressure and gas temperature which are both measured by the machine.

$\text{VCO}_2$  is calculated as the product of constant flow (Q) and the fraction of  $\text{CO}_2$  in the diluted expiratory flow ( $\text{FECO}_2$ ). Thus:

$$\text{VCO}_2 = Q \times \text{FECO}_2$$

Oxygen consumption is calculated using a modification of the Haldane transformation from the equation:

$$\text{VO}_2 = (Q/[1 - \text{FIO}_2]) \times (\text{FIO}_2 - \text{FEO}_2 - \text{FIO}_2 \times [\text{FECO}_2 - \text{FICO}_2])$$

Where  $\text{FEO}_2$  and  $\text{FECO}_2$  are the fractions of oxygen and  $\text{CO}_2$  in the mixed expiratory gas flowing through the monitor.

### *Mechanical Ventilation*

During mechanical ventilation inspired gas is sampled from the inspiratory circuit and all expired gas is collected via tubing from the common gas outlet of the ventilator from which it passes into a mixing chamber (figure 2(2)). The respiratory quotient (RQ) is calculated from inspiratory and expiratory gas fractions alone, using a formula derived using the Haldane transformation, from measurements made at appropriate points in the system:

$$\text{RQ} = \frac{1 - \text{FIO}_2}{\frac{\text{FIO}_2 - \text{FEO}_2}{\text{FECO}_2} - \text{FIO}_2}$$



VCO<sub>2</sub> is calculated as the product of the constant flow and the concentration of CO<sub>2</sub> downstream from the mixing chamber. The VO<sub>2</sub> is subsequently calculated from RQ and VCO<sub>2</sub> from the equation:

$$VO_2 = VCO_2/RQ$$

### *Correction for humidity*

Water vapour in respiratory gases or dry calibration gases is balanced with ambient air using a water trap and Nafion tubing. With this system the humidity of analysed gases is equalised with ambient air prior to measurements. Thereafter, gas fractions are expressed at Standard Temperature and Pressure.

### *Calibration*

Calibration of the Deltatrac system occurs at 3 levels. First, during use the machine performs baseline checks for CO<sub>2</sub> and O<sub>2</sub> every 10 minutes. Correction for inspired CO<sub>2</sub> fraction is made by assuming that the CO<sub>2</sub> fraction of the oxygen/air mixture decreases linearly from 0.04 to 0% as FIO<sub>2</sub> changes from 21 to 100%. Second, prior to each use the machine is calibrated against a standard gas mixture (in the present studies 95% O<sub>2</sub> and 5% CO<sub>2</sub>) and ambient barometric pressure (measured with an anaeroid barometer). Third, approximately every 3-6 months the accuracy of the flow generator is checked using an alcohol burn. A *qualitative* alcohol burn checks the overall accuracy of the machine and is quick and simple; the RQ measured by the machine should be 0.67. A *quantitative* burn of an accurately measured volume of pure alcohol, which will produce a predictable volume of CO<sub>2</sub>, can be used to make fine adjustment to the flow generator. The drift in flow generator calibration has been shown to be negligible over 3 months. Gas injection techniques using CO<sub>2</sub> and/or N<sub>2</sub> can also be used to simulate VCO<sub>2</sub> and VO<sub>2</sub> in order to calibrate the flow generator.



Figure 2.1: Schematic drawing illustrating measurement system of Deltatrac metabolic monitor in canopy mode.

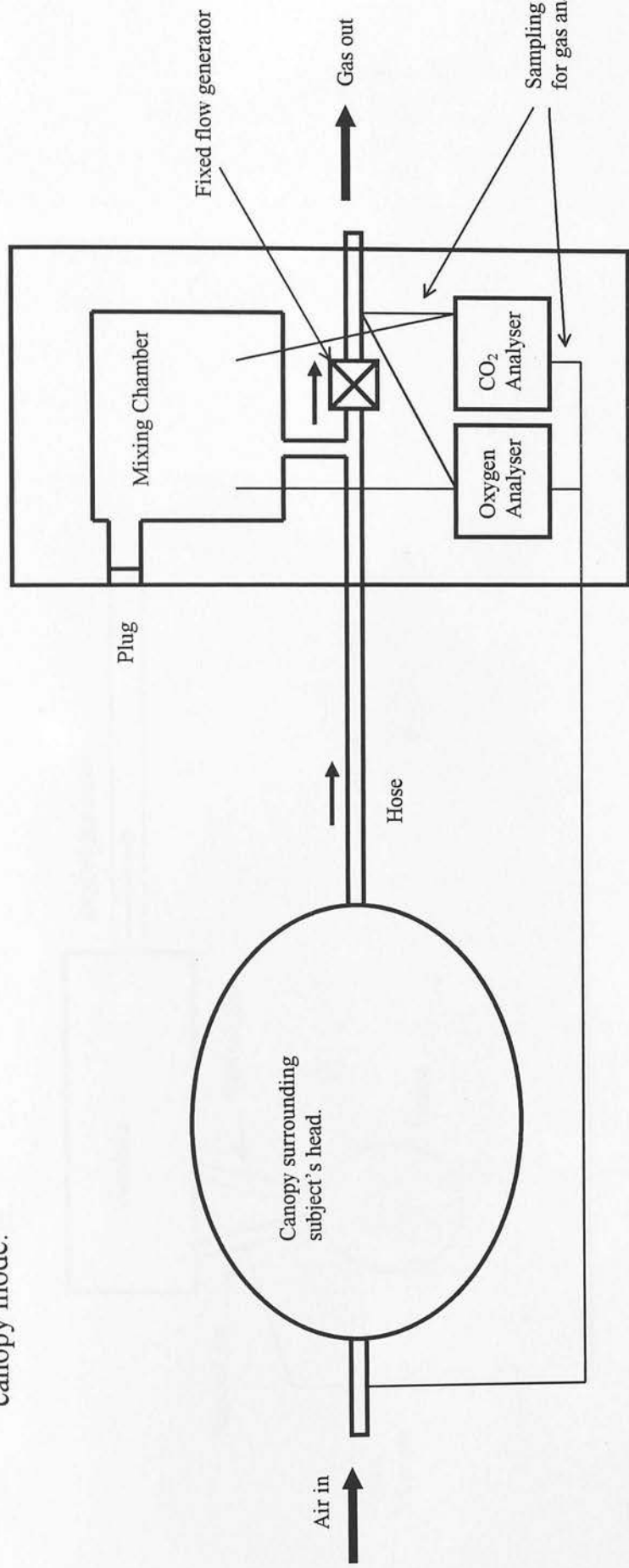
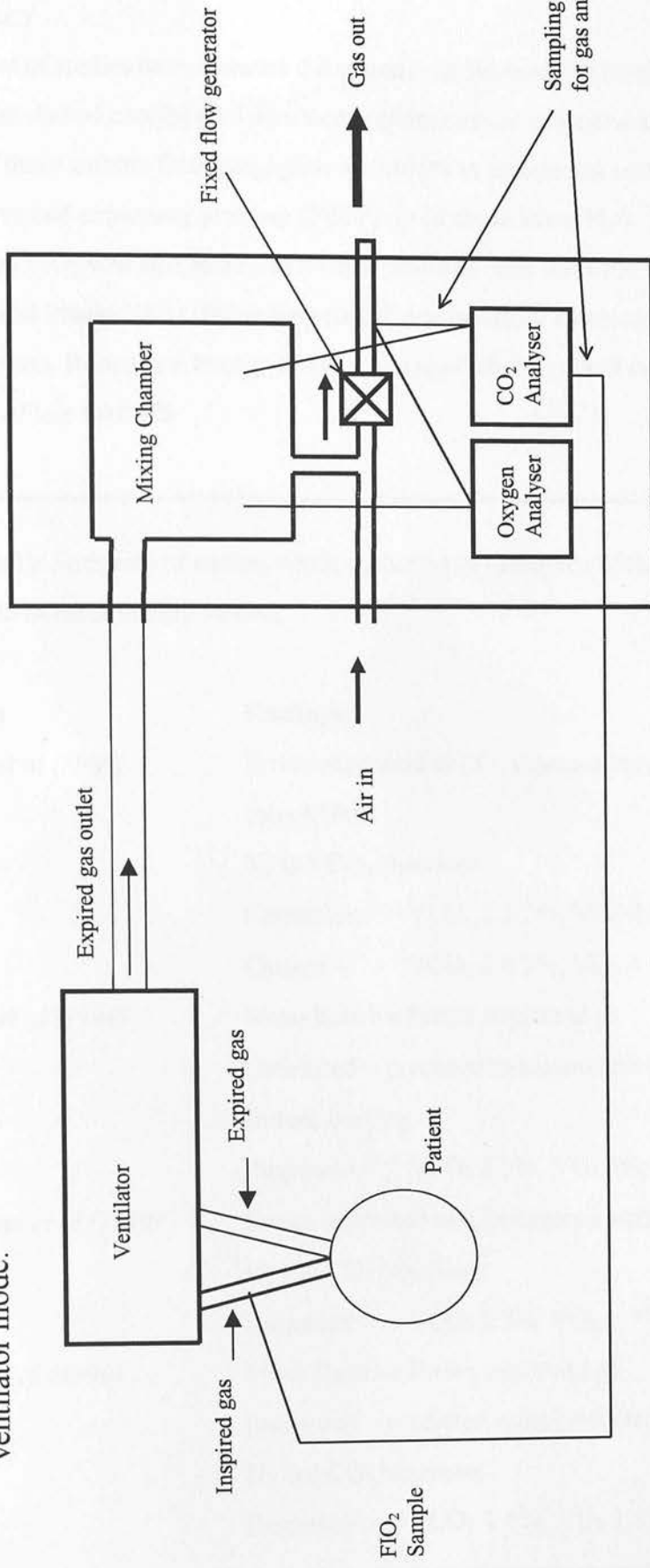


Figure 2.2: Schematic drawing illustrating measurement system of Deltatrac metabolic monitor in ventilator mode.



ACCURACY

A number of studies have assessed the accuracy of the machine in laboratory studies and under clinical conditions. Laboratory validations are summarised in table 2(1). Most of these authors found negligible inaccuracy in association with increasing levels of positive end-expiratory pressure (PEEP) up to about 20cm.H<sub>2</sub>O. The effect of increasing FIO<sub>2</sub> was also small and relative errors of <5% occurred even at FIO<sub>2</sub> 0.8 (Ronco and Phang 1991). Using lung model simulations of increases in oxygen consumption, Ronco and Phang (1991) found the Deltatrac could detect changes with an error of less than 1%.

TABLE 2(1): Summary of studies which evaluated the accuracy of the Deltatrac metabolic monitor in lung models.

Authors	Findings
<i>Takala et al (1989)</i>	Errors expressed as (1 – measured/predicted value).100 N <sub>2</sub> and CO <sub>2</sub> injections Respirator: VCO <sub>2</sub> 2 ± 2%, VO <sub>2</sub> 4 ± 4% Canopy: VCO <sub>2</sub> 3 ± 2%, VO <sub>2</sub> 4 ± 2%
<i>Makita et al (1990)</i>	Mean Relative Errors expressed as (measured – predicted value/predicted value).100 Butane burning Respirator: VCO <sub>2</sub> 2.9%, VO <sub>2</sub> 4%, RQ 4%
<i>Weissman et al (1990)</i>	Errors expressed as ± (measured/predicted value).100 N <sub>2</sub> and CO <sub>2</sub> injections Respirator: VCO <sub>2</sub> ± 7%, VO <sub>2</sub> ± 7%
<i>Phang et al (1990)</i>	Mean Relative Errors expressed as (measured – predicted value/predicted value).100 N <sub>2</sub> and CO <sub>2</sub> injections Respirator: VCO <sub>2</sub> 1.5%, VO <sub>2</sub> 1.9%

The most detailed clinical validation in ventilated patients was carried out by Tissot and colleagues (1995) who compared  $\text{VO}_2$  and  $\text{VCO}_2$  by the Deltatrac with measurements made using a mass spectrometer and with the Douglas bag method in ventilated critically ill patients. The Deltatrac gave values which agreed closely with measurements with either of these methods and any disparity was clinically insignificant. These authors also examined the effect on  $\text{VO}_2$  accuracy of fluctuation in  $\text{FIO}_2$  during the inspiratory cycle with different ventilators and concluded that the Servo C ventilators performed best because of the presence of a mixing chamber.

#### CALCULATION OF ENERGY EXPENDITURE

Energy expenditure is calculated from measured  $\text{VO}_2$  and  $\text{VCO}_2$  using the formula:

$$\text{EE (kJ.min}^{-1}\text{)} = 14.98 \text{ VO}_2 \text{ (L.min}^{-1}\text{)} + 6.06 \text{ VCO}_2 \text{ (L.min}^{-1}\text{)} - 0.092$$

(Bursztein et al, 1977, 1989)

#### SUMMARY

The Deltatrac metabolic monitor is an automated open circuit indirect calorimeter designed for measuring  $\text{VO}_2$ ,  $\text{VCO}_2$ , RQ, and energy expenditure in spontaneously breathing and mechanically ventilated patients. When used appropriately it has been demonstrated to have good accuracy in lung models and in the clinical setting. Accuracy relies on correct calibration, an absence of leaks, and steady state conditions for gas exchange.

# N-ACETYLCYSTEINE AND OXYGEN KINETICS IN FULMINANT HEPATIC FAILURE

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### OBJECTIVES

The primary objectives of the studies performed in this chapter were:

- 1) To explore the measurement errors associated with the Fick method and indirect calorimetry when used to determine oxygen consumption in patients with fulminant hepatic failure.
- 2) To document the haemodynamic effects of N-acetylcysteine in patients with severe fulminant hepatic failure during the first 5 hours of the standard infusion regimen.
- 3) To examine the relationship between oxygen delivery, oxygen consumption and oxygen extraction during N-acetylcysteine infusion in these patients.
- 4) To examine the effect of N-acetylcysteine on indirect markers of impaired tissue perfusion and hypoxia (lactate and acid-base status).
- 5) To explore the relationship between the physiological effects of N-acetylcysteine and plasma drug concentrations.

### BACKGROUND

#### N-acetylcysteine and paracetamol poisoning

The drug N-acetyl-L-cysteine is the treatment of choice for paracetamol hepatotoxicity, which occurs most frequently as a result of self-poisoning (Vale and Proudfoot 1995). Protection by the drug is dependent on early administration following paracetamol ingestion and is mediated primarily via replenishment of hepatic glutathione stores (Vale and Proudfoot 1995). Early reports indicated complete protection from hepatotoxicity, renal failure and death when N-acetylcysteine was administered within 8 hours of paracetamol ingestion, with a progressive reduction in efficacy between 8 and 15 hours (Prescott et al 1979). Treatment given more than 15 hours after ingestion was initially thought to be

ineffective. Subsequent studies have confirmed the protective effect of the drug when given within 10 hours of paracetamol ingestion but the efficacy of treatment given between 10 and 24 hours is less clearly established (Smilkstein et al 1988, Smilkstein et al 1991). During this period delay in N-acetylcysteine administration is associated with more severe liver damage and, in comparison with historical controls, case fatality rates were significantly reduced in patients who received the drug (Vale and Proudfoot 1995). The clinical benefit of late administration of N-acetylcysteine was initially questioned because of anaphylactoid reactions in up to 15% of cases (Bateman et al 1984, Mant et al 1984, Chan et al 1994), and a possible detrimental effect in some animal studies (Banda and Quart 1987). However, these potential adverse effects have proved clinically irrelevant (Parker et al 1990, Beckett et al 1990), and it is currently recommended that N-acetylcysteine is administered if more than 8 hours have elapsed from paracetamol ingestion and  $>150\text{mg.kg}^{-1}$  were ingested (Vale and Proudfoot 1995).

### **Glutathione and N-acetylcysteine**

Glutathione is a tripeptide composed of the amino acids glutamic acid, cysteine and glycine. It is the most widespread cellular thiol, occurs in virtually all mammalian cells, and is synthesised intracellularly via the  $\gamma$ -glutamyl cycle (Meister 1984, 1988)(figure 3.1). The glutathione redox cycle catalyses interconversion between the reduced (GSH) and oxidised (GSSG) form of the compound such that the vast majority of cellular glutathione is in the reduced form (ratio reduced to oxidised 100:1). GSSG is actively reduced to GSH by the enzyme *glutathione reductase*, with NADPH as cofactor, either within cells themselves, or in the liver following transport into the circulation. Cellular levels of glutathione are regulated via interrelated mechanisms involving membrane transport of precursor amino acids, intracellular synthetic activity, feedback mechanisms, and intracellular complexing of GSH (Deneke and Fanberg 1989). The liver is the primary exporter of GSH for use by other organs (primarily lung and kidney) and the availability of cysteine is the rate limiting step for glutathione synthesis. Cysteine is not an essential amino acid in

humans as it can be synthesised from methionine, but although cysteine synthesis occurs *in vivo*, dietary supplementation or direct intravenous administration appears to improve glutathione concentrations in both animals and humans (Beutler 1989). In animal models hepatic cysteine and glutathione concentrations are dependent on the dietary intake of cysteine, and exogenous supply is important in humans particularly following acute depletion (Baumann et al 1988). Therapeutic administration of cysteine is problematic because preparations are unstable (cysteine is rapidly oxidised to the relatively insoluble compound cystine) and high plasma concentrations have neurotoxic effects.

Glutathione is an antioxidant concerned primarily with biological defence against a wide variety of potentially toxic agents of both exogenous and endogenous origin. It serves either as an obligatory substrate or a cofactor in enzymatic reactions which are essential to maintain cell viability. *Glutathione peroxidase* catalyses the conversion of hydrogen peroxide, an important by-product of cellular metabolism, to water using GSH as a hydrogen ion donor. Hydrogen peroxide is a potential precursor of reactive oxygen species which, if uncontrolled by antioxidant defences, cause widespread cellular injury. *Glutathione thioltransferase* and related enzymes catalyse the reduction of sulphhydryl groups in many proteins which require to be kept in the reduced form in order to function correctly, using GSH as substrate.

N-acetylcysteine is a synthetic derivative of cysteine (figure 3(2)). It was originally developed as a mucolytic agent for inhalational administration, acting via disruption of disulphide bonds in mucus thereby reducing viscosity (Scheffner 1963). It was subsequently shown to be effective orally and has been used in the treatment of chronic obstructive pulmonary disease and cystic fibrosis (Boman et al 1983, Mitchell and Elliot 1982). N-acetylcysteine can function as a precursor of cysteine which is the basis of its therapeutic efficacy in the treatment of conditions in which cysteine and glutathione are depleted, and in this respect it is often considered an antioxidant. Human studies have shown that N-acetylcysteine is capable of increasing cysteine and glutathione concentrations in the plasma and lungs of patients with chronic



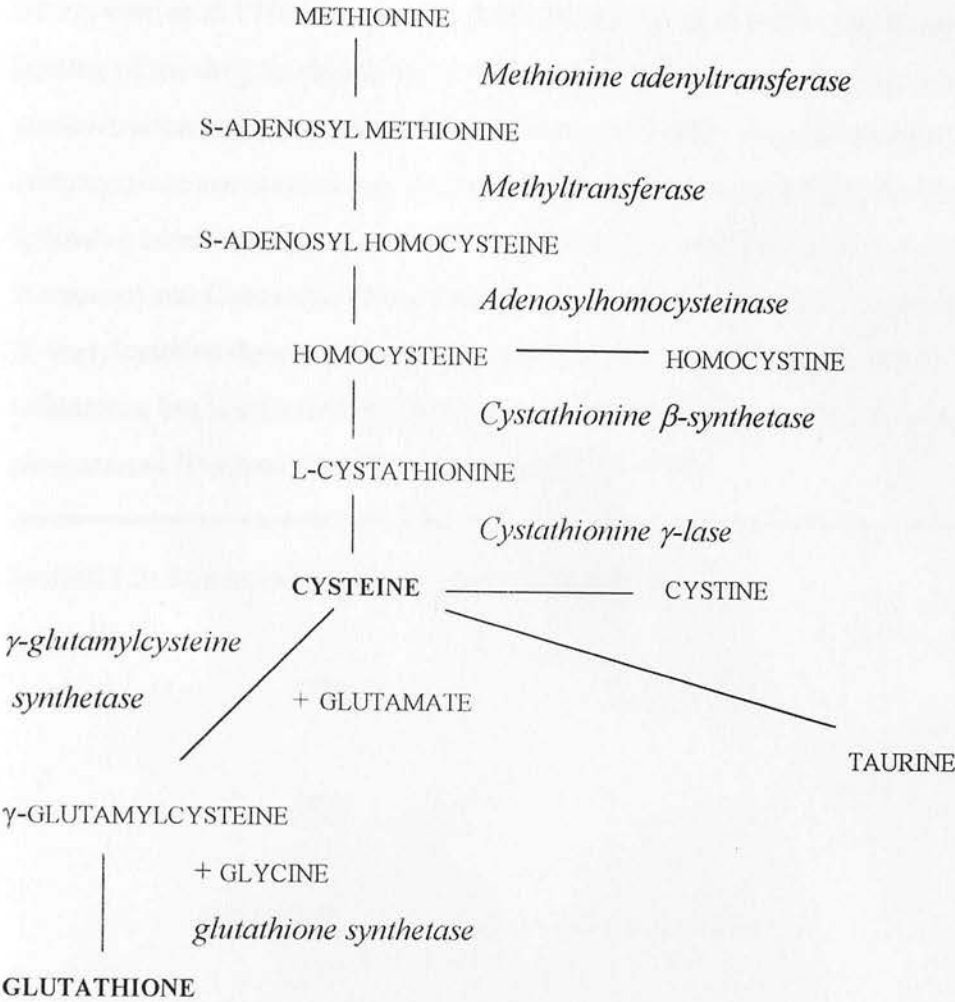
obstructive pulmonary disease, idiopathic pulmonary fibrosis, and ARDS, conditions in which antioxidant defences may be chronically or acutely depleted (McNee et al 1991, Bridgeman et al 1994, Meyer et al 1995, Bernard et al 1997).

Reactive metabolites of paracetamol, formed in the liver and kidney, are detoxified by reduced glutathione (Flanagan and Meredith 1991). Depletion of intracellular glutathione, as occurs following paracetamol overdose, results in accumulation of these reactive metabolites (primarily N-acetylbenzoquinoneimine) which are potent oxidising agents. These probably mediate hepatic and renal injury by binding covalently to cellular macromolecules. Animal studies indicate that the protective effect of N-acetylcysteine is mediated primarily via glutathione production following conversion *in vivo* to cysteine (Miners et al 1984). These findings are supported in humans in whom N-acetylcysteine has been shown to increase depleted plasma cysteine and glutathione concentrations following ingestion of paracetamol (Burgunder et al 1989). It is also hypothesised that N-acetylcysteine may have some direct antioxidant activity in this setting (Vale and Proudfoot 1995). The efficacy of N-acetylcysteine in treating paracetamol-induced hepatotoxicity has led to interest in its use in many other conditions in which antioxidant depletion and oxidant stress are thought to be important. These are considered later in this thesis.

### **N-acetylcysteine metabolism and pharmacokinetics.**

The metabolism and clinical pharmacology of N-acetylcysteine are incompletely understood. The drug exists in a variety of different forms in the plasma, and metabolism gives rise to a number of products (Olsson et al 1988)(figure 3(2)). Despite the widespread use of N-acetylcysteine over 30 years there are few pharmacokinetic or pharmacodynamic studies in animals or humans. This has resulted in part from methodological difficulties in measuring plasma concentrations of the drug and its major metabolites. Pharmacokinetic studies have used radiolabelled N-acetylcysteine (Scheffner et al 1966, Bonanomi and Gazzaniga 1980), or various techniques of gas-liquid or high performance liquid chromatography (Morgan et al 1983, Lewis et al 1985, Cotgreave and Moldeus 1987, Johansson and Westerlund

FIGURE 3.1: Biochemistry of cysteine and glutathione. Enzymes shown in italics.

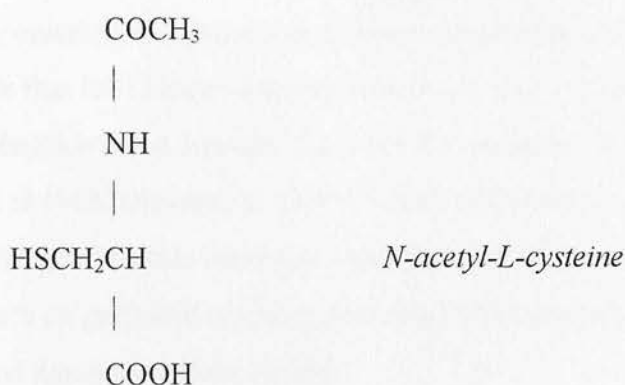


1986). With these techniques it has been shown that N-acetylcysteine may be present in plasma in intact reduced form (the parent drug) or in various oxidised forms (Olsson et al 1988). These oxidised forms result from reactions between N-acetylcysteine molecules to form N,N'-diacetylcysteine, with low molecular weight thiols such as cysteine or glutathione, or with the thiol groups of plasma proteins (figure 3(2)). Following a single intravenous dose of N-acetylcysteine in healthy

volunteers the plasma clearance of reduced N-acetylcysteine is rapid and biphasic with most of the drug cleared within 1 hour (Olsson et al 1988, Burgunder et al 1989). Oxidised forms, and total concentrations of the drug with its various metabolites, are cleared much more slowly with a terminal half life of 2-6 hours in published studies (Borgstrom et al 1986, Olsson et al 1988, Burgunder et al 1989). The disulphide binding of the drug to plasma and tissue proteins increases progressively following administration and is probably >50% (Olsson et al 1988). The main metabolites of N-acetylcysteine are cysteine and cystine which increase in concentration in plasma following administration of the drug (Scheffner et al 1966, Rodenstein et al 1978, Bonanomi and Gazzaniga 1980). Deacetylation probably occurs primarily in the liver. N-acetylcysteine does not alter plasma glutathione concentrations in healthy volunteers, but is effective in replenishing them following acute depletion by paracetamol (Poulsen et al 1993, Burgunder et al 1989).

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FIGURE 3.2: Structure and metabolites of N-acetylcysteine.



Oxidation products occurring *in vivo* following administration:

- N,N'-Diacetylcysteine
  - N-Acetylcysteine-cysteine
  - N-Acetylcysteine-protein
  - N-Acetylcysteine-glutathione
-

Various dosing regimens have been used for the drug. Following oral administration absorption is rapid, but the bioavailability is low (less than 10%) because of high first pass intestinal and hepatic metabolism (Borgstrom et al 1986). For treatment of paracetamol-induced hepatotoxicity intravenous administration is recommended (Vale and Proudfoot 1995). The intravenous administration regimen used in most studies is identical, or very similar to, that described by Prescott et al (1977, 1979). This regimen was designed for treatment of paracetamol overdose and gives a very large dose of drug in a short time ( $150\text{mg.kg}^{-1}$  over 15 minutes) in order to rapidly replenish hepatic and renal glutathione. Thereafter  $50\text{mg.kg}^{-1}$  is given over 4 hours followed by  $100\text{mg.kg}^{-1}$  over 16 hours. This regimen was originally chosen arbitrarily (Prescott et al 1989) and the plasma concentration of N-acetylcysteine required for maximum therapeutic benefit is unknown in patients both following paracetamol overdose and in the other diagnostic groups in which it has been used. A pharmacokinetic study in patients presenting after paracetamol overdose demonstrated very high peak plasma concentrations of total N-acetylcysteine which declined rapidly after the loading dose was completed (Prescott 1989). Reduced N-acetylcysteine, cysteine, and glutathione concentrations were not measured. These studies indicate that the volume of distribution of the drug (all forms) is about  $500\text{ml.kg}^{-1}$ , the clearance about  $3\text{ml.min}^{-1}.\text{kg}^{-1}$ , and the elimination half life about 6 hours (Borgstrom et al 1986, Olsson et al 1988, Prescott et al 1989). Up to 30% of the drug is cleared unchanged in urine, the rest is cleared by metabolism (Borgstrom et al 1986). There are no published studies concerning N-acetylcysteine kinetics in patients with established fulminant hepatic failure.

## MATERIALS AND METHODS

### *Study Design*

This was designed as a prospective randomised controlled study. In the only previous study in this area Harrison et al (1991) observed a highly significant increase in oxygen delivery 30 minutes after starting N-acetylcysteine in 12 patients with paracetamol-induced fulminant hepatic failure (mean increase  $119\text{ml.min}^{-1}.\text{m}^{-2}$ , 95%

confidence intervals 51-196). An increase in oxygen delivery of  $100 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  in response to a therapeutic intervention is widely considered clinically significant in the oxygen kinetics literature (equivalent to an increase in cardiac output of about  $0.7\text{-}1.0 \text{ l} \cdot \text{min}^{-1}$  assuming normal arterial oxygen content). From rates of admission to the Scottish Liver Transplant Unit in 1994 of patients with fulminant hepatic failure who subsequently required admission to the intensive care unit, I anticipated approximately 20 patients might be recruited over the 18 month period available for the study. Harrison et al (1991) did not include a control group in their study but I considered control patients essential for proper evaluation of the drug. In order to achieve the same power to study a mean increase of at least  $100 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ , I chose to randomise 14 patients to receive N-acetylcysteine and 7 to receive placebo infusions. This was done by means of sealed envelopes at the time of study entry.

### *Patient population*

Patients were studied between March 1995 and July 1996. All studies were carried out within 24 hours of admission to the Intensive Care Unit at the Royal Infirmary of Edinburgh. Admission criteria for the study were as follows:

- 1) Diagnosis of fulminant hepatic failure.
- 2) Consent for inclusion in the study from relatives.
- 3) Patient had either not previously received N-acetylcysteine during this illness, or if they had done so it had been discontinued at least 24 hours before study entry. This time period represented approximately 4 half-lives using published data in healthy individuals and in patients studied within 16 hours of paracetamol overdose.
- 4) No history of adverse reaction to N-acetylcysteine.
- 5) Patient required sedation, tracheal intubation, and mechanical ventilation for clinical management.
- 6) Patient required insertion of an arterial catheter and pulmonary artery catheter for clinical management.

All patients were sedated (propofol and alfentanil infusions) and paralysed (atracurium infusion) and the lungs ventilated using a Servo 900C or 900D ventilator (Siemens-Elima, Soln, Sweden) to achieve a  $\text{PaCO}_2$  of between 3.5 and 5.0 kPa. Changes in ventilator settings were only made if clinically indicated. The  $\text{FIO}_2$  was adjusted to achieve an arterial  $\text{PaO}_2$  of 15-25 kPa and then remained unchanged during the study period. Prior to commencing the study patients were resuscitated with 0.9% NaCl solution, colloid solutions, or red cell concentrate until the pulmonary artery wedge pressure was  $\geq 8\text{mmHg}$  and the haemoglobin concentration was  $\geq 8\text{ g.dl}^{-1}$ . This figure was chosen as a compromise between the beneficial effects for tissue perfusion of aggressive fluid loading and the potentially detrimental effects of fluid overload on cerebral perfusion and cerebral oedema. If clinically indicated, noradrenaline was then administered by infusion and titrated to achieve a mean arterial pressure of  $\geq 70\text{mmHg}$ . During the study period colloid infusion was administered to maintain the pulmonary artery wedge pressure at the baseline value. Changes in noradrenaline therapy were only made if the mean arterial pressure decreased below 70mmHg. Patients requiring renal replacement therapy were established on continuous venovenous hemofiltration at least 2 hours prior to starting the study. In all cases prostacyclin ( $2\text{-}4\text{ng.kg}^{-1}.\text{min}^{-1}$ ) was used as an anticoagulant and the infusion rate remained unchanged throughout the study period. During the study blood glucose concentration was measured hourly and maintained between 4 and 6  $\text{mmol.l}^{-1}$  by dextrose infusion. No patients received enteral or parenteral nutrition during the 24 hours prior to or during the study.

### *Data collection*

Arterial blood pressure was monitored with an indwelling radial or femoral artery catheter. Cardiac output and central venous pressure were monitored using a continuous cardiac output (CCO) pulmonary artery catheter (Baxter Vigilance system, Irvine, CA, USA). Correct positioning of the catheter was confirmed radiologically before the study commenced. This system provides a semicontinuous estimation of cardiac output by adding pulses of heat to right ventricular blood via a thermal filament every 30-60 seconds. The resulting increase in blood temperature is





sensed by a thermistor at the catheter tip and cardiac output is calculated using the thermodilution principal (Munro et al 1994). The machine displays a running average of measurements made over the past 3-6 minutes. Haemodynamic data were recorded to computer during the study period from the monitoring systems (Hewlett Packard Merlin, Palo Alto, CA, USA; Baxter Vigilance).

### *Determination of oxygen consumption*

Direct gas exchange measurement:  $\text{VO}_2$  was measured with the Deltatrac metabolic monitor. For the remainder of the thesis this is termed  *$\text{VO}_2$  calorimetry*.

Calculation of oxygen consumption: The Fick method was used to calculate oxygen consumption index using the standard formula (refer to introduction). For the remainder of this thesis this is termed  *$\text{VO}_2$  Fick*.

A mean value for cardiac index was taken over a 10 minute period from the CCO recording for the calculation of oxygen consumption by the Fick method. This time period was chosen as a balance between maximising the number of averaged data points, and therefore the accuracy of cardiac output measurements, and avoiding spontaneous variations in cardiac output. At the midpoint of this period 2 ml samples of systemic and pulmonary arterial blood were drawn. The presence of an unwedged pulmonary artery pressure trace was confirmed prior to sampling and the mixed venous sample was aspirated over at least 30 seconds. Blood samples were analysed within 5 minutes of collection using an IL 482 cooximeter and an IL BGE 1400 series acid-base analyser (Instrumentation Laboratories, Lexington, MA, USA). The manufacturer quotes the accuracy (95% confidence intervals) of measurements as  $\pm 1\%$  (haemoglobin oxygen saturation),  $\pm 0.3 \text{ g.dl}^{-1}$  (haemoglobin), and  $\pm 0.22 \text{ kPa}$  (oxygen tension, over the normal physiological range).

### *Study protocol*

The study commenced after a stable baseline period of at least 30 minutes during which the range of cardiac output and  $\text{VO}_2$  values was less than 10% of the mean for the period. Patients in the N-acetylcysteine group received a loading dose of N-



acetylcysteine followed by an infusion according to the standard regimen widely used in the treatment of paracetamol overdose (Prescott et al 1979, 1989) and identical to the regimen used in the study by Harrison et al (1991): 150mg.kg<sup>-1</sup> body weight in 200 ml 5% dextrose over 15 minutes, followed by 50 mg.kg<sup>-1</sup> in 500 ml 5% dextrose over 4 hours, followed by 100mg.kg<sup>-1</sup> in 1 litre over 16 hours. Patients in the control group received volume-matched control infusions of 5% dextrose alone.

The following study points were chosen for blood sampling over the 5 hour study period: baseline (prior to administration of N-acetylcysteine), 30, 60, 120, 180, and 300 minutes after starting the infusion. At each study point blood was sampled from the arterial catheter and pulmonary artery catheter for determination of oxygen delivery and Fick-derived oxygen consumption. Arterial blood was drawn for acid-base, lactate measurements, and for measurement of plasma N-acetylcysteine concentrations

Whole blood lactate concentration was measured using a YSI 2300 Stat Plus analyser (Yellow Springs Instrument Co, Yellow Springs, Ohio). A further sample was spun and the serum frozen at -60°C for subsequent determination of N-acetylcysteine concentration. Ten minute averages were calculated for VO<sub>2</sub>, cardiac index, mean arterial pressure, and central venous pressure. DO<sub>2</sub>, OER, and systemic vascular resistance index (SVRI) were calculated using standard formulae (see Appendix 1). Data were indexed against body surface area.

#### *Measurement of N-acetylcysteine concentrations.*

N-acetylcysteine concentrations were batch analysed using the high performance liquid chromatographic method described by Lewis et al (1984) with modifications described subsequently (Lewis et al 1985, Holdiness et al 1986). This work was carried out in the Edinburgh University Department of Clinical Chemistry by Dr David Jarvie. Plasma was diluted with water as required, and N-glycylglycine pre-reacted with 2,4-dinitrofluorobenzene was used as the internal standard. After reaction with dinitrofluorobenzene, the mixture was acidified with 0.5 ml of 1M HCl before

extraction into ether. The glycylglycine and N-acetylcysteine derivatives were eluted in 2.8 and 5.3 minutes respectively. This method measures total oxidised and reduced N-acetylcysteine together with drug bound to other thiols and proteins.

## RESULTS

### *Patient demographics and clinical data.*

*Numbers Studied:* In the available time 18 patients were enrolled into the study. Randomisation resulted in 11 allocations to the N-acetylcysteine group and 7 to the control group.

*Demographics and clinical data:* Patient demographics, and baseline haemodynamic and gas exchange data are shown in table 3(1) . All patients had severe fulminant hepatic failure indicated by the prolongation of the prothrombin time, severity of encephalopathy, and high incidence of renal failure. Patients were characterised by a high cardiac output, high mixed venous oxygen saturation, low oxygen extraction ratio, and low peripheral vascular resistance.

### **Analysis of Data**

The results of this study are considered in 2 separate sections each with a discussion:

#### **SECTION 1:**

*Comparison between the reverse Fick method and indirect calorimetry for determining oxygen consumption in patients with fulminant hepatic failure.*

#### **SECTION 2:**

*Analysis of the effect of N-acetylcysteine on oxygen transport and uptake in patients with fulminant hepatic failure.*

TABLE 3.1: Patient characteristics and baseline measurements. All values are mean (sd) unless otherwise stated. No significant differences in physiological variables between groups.

	N-acetylcysteine Group	Placebo Group
Patients (no.)	11	7
Age (yr) (mean [range])	27 (16-65)	31 (15-54)
Aetiology: Paracetamol	10	6
NANB hepatitis	1	1
Prothrombin time at time of study (sec.) (mean [range])	118 (59-205)	120 (60-200)
Renal failure (creatinine >300µmol.l <sup>-1</sup> ) (no.)	8	3
Patients requiring noradrenaline infusion (no.)	6	1
FIO <sub>2</sub>	0.39 (0.09)	0.34 (0.08)
PaO <sub>2</sub> (kPa)	17.6 (4.8)	19.6 (4.2)
PaCO <sub>2</sub> (kPa)	4.6 (0.5)	4.5 (0.6)
Haemoglobin concentration (g.l <sup>-1</sup> )	102 (13)	104 (19)
Cardiac Index (l.min <sup>-1</sup> .m <sup>-2</sup> )	5.6 (1.8)	4.7 (0.9)
MAP (mmHg)	81 (16)	84 (8)
SVRI (dyne.sec.cm <sup>-5</sup> .m <sup>-2</sup> )	1124 (525)	1381 (360)

## Comparison between the reverse Fick method and indirect calorimetry measurements of oxygen consumption in patients with fulminant hepatic failure.

### Data

In 14 patients 6 data pairs were collected. In 4 patients only 5 data pairs were collected giving a total of 104 data pairs. Missing data points occurred because of acute increases in intracranial pressure requiring altered ventilation and mannitol therapy (2 patients), severe hypotension requiring rapid changes in noradrenaline dose (1 patient), and transfer to the operating theatre for liver transplantation (1 patient).

### *Agreement between methods of determining $VO_2$*

The agreement between the two methods of measuring  $VO_2$  was compared using the Bland and Altman method (1986) which estimates the bias between the methods and the limits within which most differences are expected to lie. I determined whether the bias between the methods was dependent on the size of the  $VO_2$  measurement by calculating the correlation coefficient between the bias and the mean oxygen consumption for the 18 patients.

It could not be assumed that the oxygen consumption of individual patients remained constant throughout the study period so the *repeatability* of the two methods of measurement could not be assessed since this would attribute all differences to measurement error. I therefore compared the *reproducibility* of the two methods. The reproducibility of each method of measurement was assessed using one way analysis of variance (ANOVA) to calculate the *within patients standard deviation* (WPSD,  $S_w$ ) of oxygen consumption measurements for the 18 patients (Bland and Altman 1996). This is a measure of the dispersion of the measurements which results from both measurement errors and physiological variations in  $VO_2$  during the study period. As all data pairs were obtained simultaneously any physiological variability in  $VO_2$  applied to both methods of measurement. The *ratio* of the WPSDs for the two techniques therefore compared dispersion attributable to measurement error alone and

enabled an estimation of the *relative reproducibility* of each method of measurement to be made. A similar approach has been used previously (Hanique et al 1994b).

The dispersion of data obtained by the two methods was also illustrated by calculating the coefficient of variation ( $[SD/mean].100$ ) of  $VO_2$ Fick and  $VO_2$ calorimetry for each patient. Coefficients of variation for cardiac output for each patient over the study period were also calculated.

### *Effect of mathematical coupling*

For the patients who received N-acetylcysteine  $DO_2/VO_2$  data pairs were plotted using both the  $VO_2$ Fick and  $VO_2$ calorimetry data and the slope of the relationship with each method of measurement calculated using linear regression analysis. In order to compare data with the study of Harrison and colleagues (1991)  $DO_2/VO_2$  slopes were calculated using the 3 data pairs from the first hour of the study as well as for the entire study period. To explore changes in  $VO_2$  with respect to time rather than  $DO_2$ , pooled  $VO_2$  data using each method of measurement was plotted for the N-acetylcysteine and control groups.

## **Results**

Cardiorespiratory data for the patients is shown in table 3.2. In most patients only minor alterations in gas exchange and acid-base status occurred during the study period (table 3.3).

### *Agreement between the methods.*

The Bland and Altman plot for the data is shown in figure 3.3. The mean bias between the methods of measurement was  $-41 \text{ ml.min}^{-1}\text{.m}^{-2}$  (95% confidence intervals  $-35$  to  $-47 \text{ ml.min}^{-1}\text{.m}^{-2}$ ) with  $VO_2$ Fick less than  $VO_2$ calorimetry, the precision (sd of the bias) was  $30 \text{ ml.min}^{-1}\text{.m}^{-2}$ , the upper limit of agreement was  $+19 \text{ ml.min}^{-1}\text{.m}^{-2}$  (95% confidence intervals  $+14$  to  $+24 \text{ ml.min}^{-1}\text{.m}^{-2}$ ), and the lower limit of agreement was  $-101 \text{ ml.min}^{-1}\text{.m}^{-2}$  (95% confidence interval  $-96$  to  $-106 \text{ ml.min}^{-1}\text{.m}^{-2}$ ). The bias varied

widely both within and between patients (table 3.4). There was no relationship between the mean bias and the mean  $\text{VO}_2$  for each of the 18 patients ( $r = 0.1$ ) indicating that the size of the measurement was unlikely to influence the bias between the methods.

Table 3.2: Cardiorespiratory data for the 18 patients with fulminant hepatic failure. All values mean (SD)[range].

Cardiac index ( $\text{L}.\text{min}^{-1}.\text{m}^{-2}$ )	5.7(0.4)	[3.4-9.5]
Systemic vascular resistance index ( $\text{Dyne}.\text{sec}.\text{cm}^{-5}.\text{m}^{-2}$ )	1245(116)	[519-2142]
SaO <sub>2</sub> (%)	99.1(0.3)	[95.4-100]
SvO <sub>2</sub> (%)	86.7(1.0)	[75.1-92.0]
Hb (g.L <sup>-1</sup> )	101(3)	[84-127]
Arteriovenous oxygen content difference ( $\text{mL}.\text{dL}^{-1}$ )	1.6(0.1)	[1.0-2.8]

*Reproducibility of the methods.*

The WPSD was  $15 \text{ ml}.\text{min}^{-1}.\text{m}^{-2}$  for the  $\text{VO}_2\text{Fick}$  data and  $7 \text{ ml}.\text{min}^{-1}.\text{m}^{-2}$  for the  $\text{VO}_2\text{calorimetry}$  data giving a ratio of 2.14. Over the study period the dispersion of measurements was greater for  $\text{VO}_2\text{Fick}$  than  $\text{VO}_2\text{calorimetry}$  in all the patients studied (figure 3.4). Cardiac output varied significantly over the period of measurement in some patients (figure 3.4). For the 18 patients, coefficients of variation for cardiac output correlated with those for both  $\text{VO}_2\text{Fick}$  ( $r = 0.51, p<0.05$ ) and  $\text{VO}_2\text{calorimetry}$  ( $r = 0.76, p<0.001$ ).



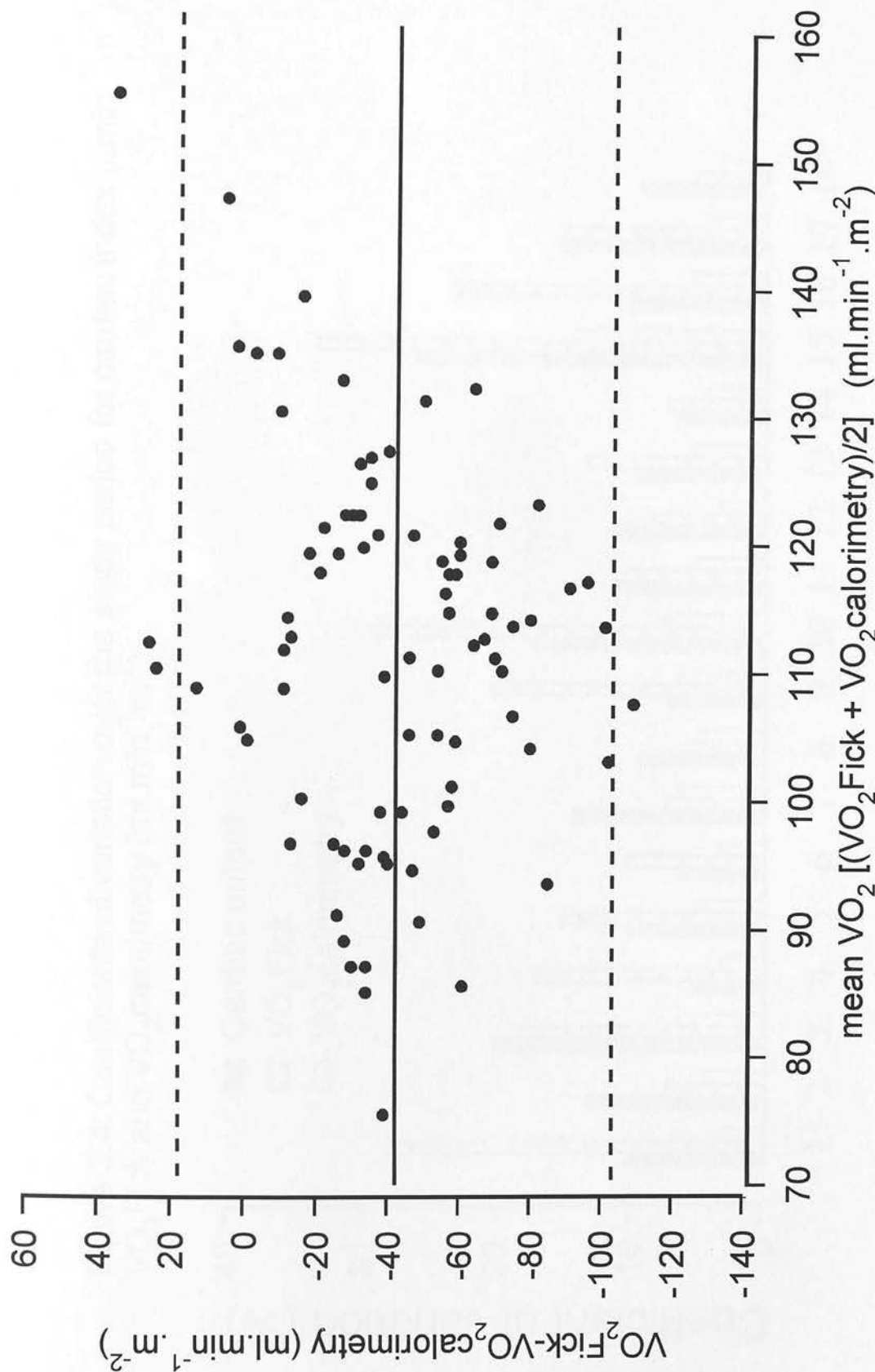


Figure 3.3: Bland and Altman plot comparing the agreement between  $VO_2$  calculated with the Fick method ( $VO_2$ Fick) and measured by indirect calorimetry ( $VO_2$ calorimetry). The mean bias between the methods (solid line) and limits of agreement (broken lines) are shown.

Figure 3.4: Coefficients of variation over the study period for cardiac index ( $\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ),  $\text{VO}_2\text{Fick}$  and  $\text{VO}_2\text{calorimetry}$  ( $\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ).

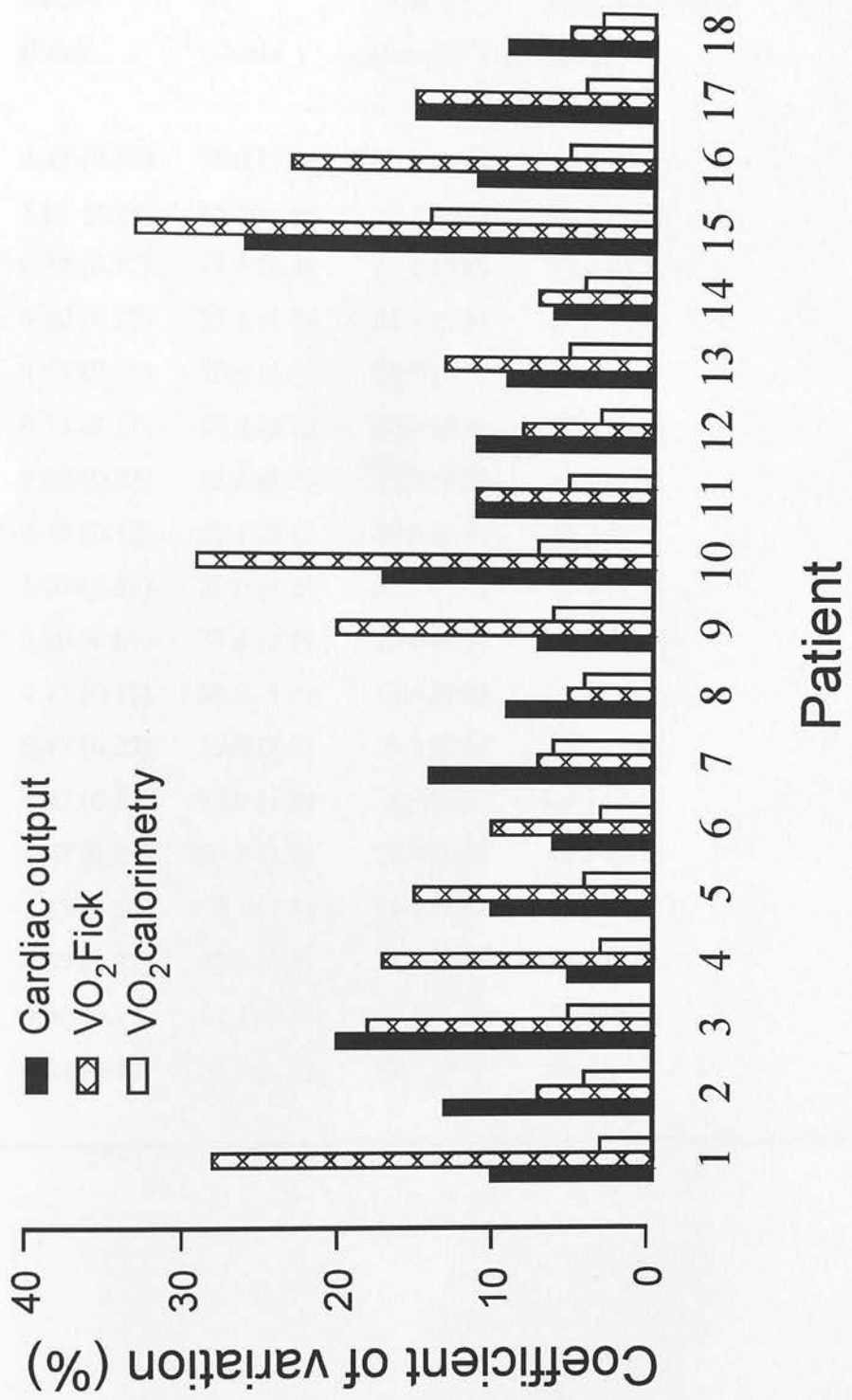


Table 3.3: Variation in arterial carbon dioxide tension ( $\text{PaCO}_2$ ), hydrogen ion concentration ( $[\text{H}^+]$ ), standard bicarbonate concentration ( $[\text{SBC}]$ ), and arterial oxygen tension to fractional inspired oxygen ratio ( $\text{PaO}_2/\text{FIO}_2$ ) in each patient during the study period. Mean (sd).

Patient	$\text{PaCO}_2$ (kPa)	$[\text{H}^+]$ (nmol.l <sup>-1</sup> )	$[\text{SBC}]$ (mmol.l <sup>-1</sup> )	$\text{PaO}_2/\text{FIO}_2$ ratio (kPa)
1	5.47 (0.34)	72.0 (1.9)	14.6 (0.6)	39.7 (2.3)
2	3.87 (0.27)	44.7 (0.8)	19.1 (0.4)	57.6 (2.5)
3	4.53 (0.27)	41.9 (1.2)	21.9 (0.4)	48.0 (9.7)
4	4.80 (0.27)	37.2 (1.5)	25.4 (0.8)	24.9 (4.9)
5	4.53 (0.34)	30.8 (1.2)	28.9 (0.7)	62 (2.4)
6	4.53 (0.13)	29.3 (0.8)	30.3 (0.8)	57.1 (2.3)
7	4.80 (0.27)	53.8 (1.5)	17.7 (1.2)	39.2 (2.3)
8	4.40 (0.13)	30.1 (2.1)	28.9 (1.4)	62.8 (2.9)
9	5.07 (0.53)	27.0 (1.2)	26.3 (1.4)	52.1 (1.7)
10	5.20 (0.67)	37.8 (3.9)	26.6 (1.0)	57.1 (12.8)
11	4.13 (0.13)	54.9 (5.3)	16.4 (1.8)	63.1 (6.7)
12	5.47 (0.27)	59.0 (2.9)	18.1 (0.5)	18.5 (2.8)
13	4.27 (0.27)	34.0 (1.5)	25.5 (0.2)	61.2 (2.4)
14	3.87 (0.27)	26.3 (1.2)	30.3 (0.4)	45.9 (6.1)
15	4.13 (0.13)	35.1 (2.6)	24.6 (1.1)	61.6 (15.1)
16	4.67 (0.27)	27.5 (1.4)	32.2 (0.9)	58.8 (8.0)
17	4.40 (0.67)	57.1 (7.5)	16.1 (1.0)	37.6 (4.7)
18	5.64 (0.43)	34.4 (1.9)	30.0 (0.3)	46.0 (1.3)

Table 3.5 shows the slopes of the  $\text{DO}_2/\text{VO}_2$  relationships for the patients who received N-acetylcysteine using either the first 3 data pairs alone or all data pairs. The spread of data around the best-fit slope was much greater for the  $\text{VO}_2\text{Fick}$  data than for the  $\text{VO}_2\text{calorimetry}$  data as indicated by the 95% confidence intervals for the slopes. Using only the first 3 data pairs the  $\text{DO}_2/\text{VO}_2\text{Fick}$  slopes were significantly greater than the  $\text{DO}_2/\text{VO}_2\text{calorimetry}$  slopes [mean 16 (sd 22) vs 2(1),  $P<0.05$ ]. There was a trend for the  $\text{DO}_2/\text{VO}_2\text{Fick}$  slopes to be greater than the  $\text{DO}_2/\text{VO}_2\text{calorimetry}$  slopes when data pairs for the entire study period were used but the difference was not statistically significant.  $\text{DO}_2/\text{VO}_2\text{Fick}$  slopes were significantly greater when only the first 3 data pairs were used than when data for the entire study period were used [16(22) vs 7(8),  $P<0.05$ ].  $\text{VO}_2\text{calorimetry}$  slopes were similar using either 3 or all data points.

When pooled data for the patients were plotted with respect to time, there was a trend for  $\text{VO}_2\text{Fick}$  data to increase during the first hour of the study period. This trend was not present for the  $\text{VO}_2\text{calorimetry}$  data (figure 3.5). However, differences between the groups were not statistically significant.

Table 3.4: Summary of values for oxygen consumption measured by indirect calorimetry ( $VO_2\text{calorimetry}$ ) and calculated by the Fick method ( $VO_2\text{Fick}$ ) in each patient (mean (sd)). The mean bias between the methods and variability which occurred over the study period are shown

Patient	$VO_2\text{calorimetry}$ (ml.min <sup>-1</sup> .m <sup>-2</sup> )	$VO_2\text{Fick}$ (ml.min <sup>-1</sup> .m <sup>-2</sup> )	Bias	Range of bias (max,min)
1	149 (5)	96 (27)	-53 (29)	-102,-16
2	140 (6)	87 (6)	-53 (5)	-59,-46
3	113 (6)	88 (16)	25 (15)	-49,-11
4	140 (4)	135 (23)	-5 (11)	-30,+35
5	159 (7)	81 (12)	-78 (14)	-96,-60
6	148 (4)	80 (8)	-69 (9)	-80,-55
7	133 (7)	109 (8)	-23 (11)	-37,-10
8	117 (4)	75 (4)	-42 (7)	-53,-32
9	106 (6)	81 (16)	-24 (10)	-39,-11
10	152 (10)	75 (22)	-77 (29)	-109,-40
11	146 (7)	73 (13)	-73 (7)	-85,-67
12	102 (3)	114 (9)	+13 (13)	-1,+26
13	126 (7)	72 (9)	-54 (7)	-61,-44
14	136 (6)	104 (8)	-31 (6)	-39,-22
15	114 (16)	91 (30)	-23 (15)	-34,+2
16	130 (6)	61 (14)	-68 (12)	-85,-52
17	122(5)	110 (17)	-12 (15)	-36,+1
Mean	131 (17)	90 (19)	-41 (27)	

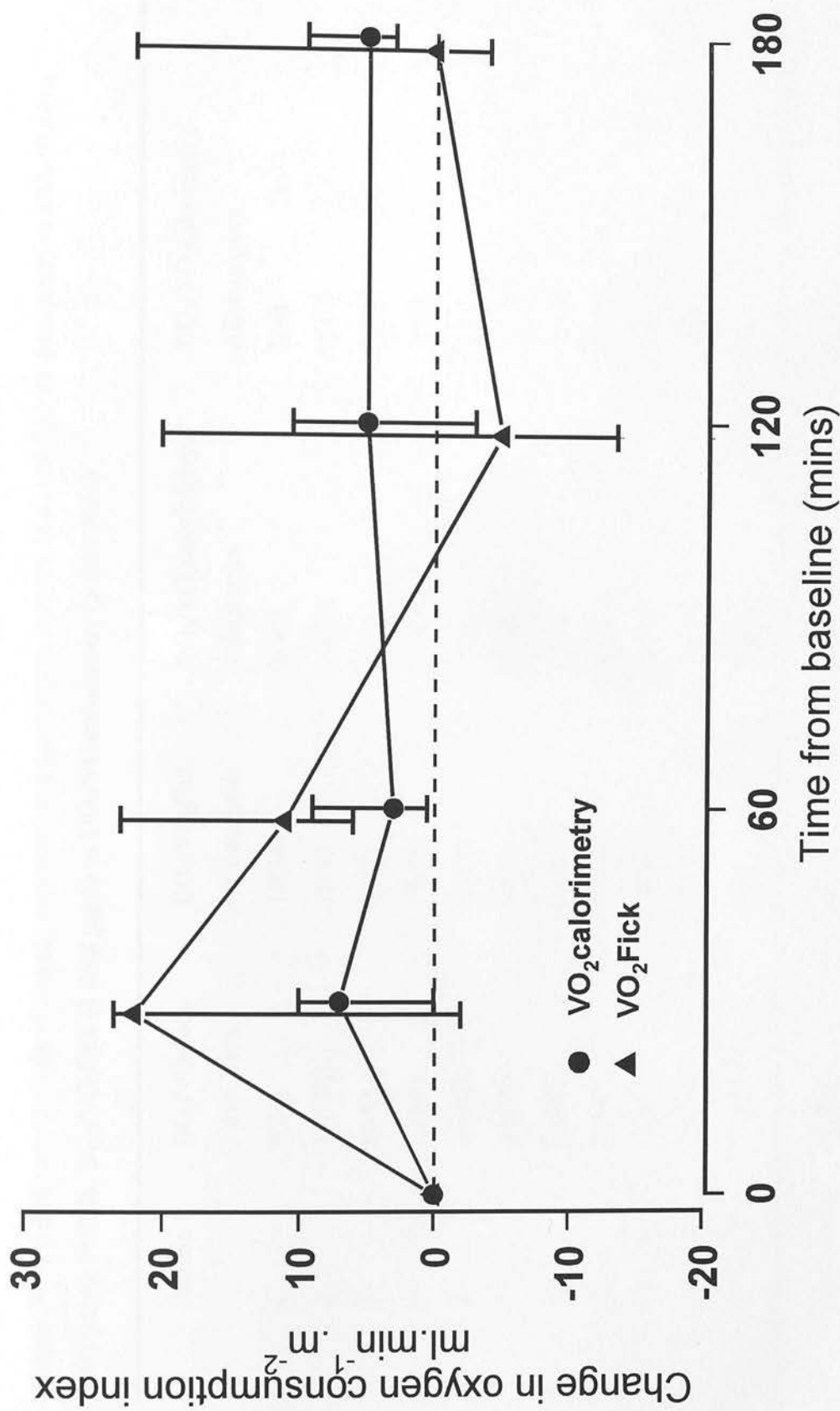


Figure 3.5: Changes in VO<sub>2</sub> during N-acetylcysteine infusion. Comparison between VO<sub>2</sub>Fick and VO<sub>2</sub> calorimetry with respect to time for the 11 patients who received N-acetylcysteine. Median (interquartile range).



Table 3.5: Slopes for the  $\text{DO}_2/\text{VO}_2\text{Fick}$  and  $\text{DO}_2/\text{VO}_2\text{calorimetry}$  data for patients who received N-acetylcysteine. All values are slopes (95% confidence intervals of slopes) expressed as a percentage.  $P<0.05$ ,  $\text{DO}_2/\text{VO}_2\text{Fick}$  (3 data pairs) vs  $\text{DO}_2/\text{VO}_2\text{Fick}$  (all data pairs);  $P<0.05$ ,  $\text{DO}_2/\text{VO}_2\text{Fick}$  (3 data pairs) vs  $\text{DO}_2/\text{VO}_2\text{calorimetry}$  (3 data pairs).

Patient	$\text{DO}_2/\text{VO}_2\text{Fick}$ 3 data pairs	$\text{DO}_2/\text{VO}_2\text{Fick}$ All data pairs	$\text{DO}_2/\text{VO}_2\text{calorimetry}$ 3 data pairs	$\text{DO}_2/\text{VO}_2\text{calorimetry}$ All data pairs
1	8(84)	10(34)	2(57)	2(6)
2	17(132)	15(7)	-6(41)	9(17)
3	6(48)	5(10)	2(1)	3(2)
4	75(80)	17(35)	-13(50)	-1(8)
5	4(169)	-2(13)	7(4)	5(2)
7	16(52)	0(12)	3(92)	-2(11)
10	23(57)	0(33)	1(24)	2(15)
11	20(7)	13(34)	8(7)	2(18)
12	-3(13)	-6(5)	1(71)	1(6)
16	23(171)	17(38)	15(22)	13(8)
17	-10(423)	6(8)	-2(6)	2(15)
Mean (sd)	16(22)	7(8)	2(1)	3(2)

The agreement between the two methods of measurement,  $\text{VO}_2\text{Fick}$  and  $\text{VO}_2\text{calorimetry}$ , was very poor in the patients studied. Using the Bland and Altman analysis the limits of agreement predicted that the two methods of measurement might differ by up to  $130 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ . Measurement errors of this magnitude are highly significant. Neither of the methods which were used could be considered a “gold standard” and the poor agreement between them may have been attributable to errors with either of the techniques or because the methods were estimating different physiological variables.

### *Errors associated with Fick calculations.*

Large errors can occur when cardiac output is determined by thermodilution using bolus injections of fluid (Stetz et al 1982, Pinsky 1990). The method used in the study was an automated thermodilution system in which errors due to injection technique are eliminated and the effect of random error is thought to be reduced by averaging multiple data points. It is generally assumed that this improves the accuracy of the method although most studies have only compared it with bolus thermodilution which is not itself a “gold standard”. Studies which have compared the Vigilance CCO system with bolus thermodilution have demonstrated good agreement between the two methods although the agreement may be worse in hyperdynamic patients particularly during periods of haemodynamic change (Mitsuo et al 1995, Boldt et al 1994, Bottiger et al 1997). Bizouarn et al (1995) showed that the repeatability of  $\text{VO}_2\text{Fick}$  was good in stable post cardiac surgery patients when cardiac output was measured with the Vigilance system and attributed this to the precision of cardiac output measurements. Despite using the same system for measuring cardiac output and taking an average measurement over 10 minutes the agreement between  $\text{VO}_2\text{Fick}$  and  $\text{VO}_2\text{calorimetry}$  was poor in patients with fulminant hepatic failure.

Cardiac output was high, all the patients were sedated and paralysed, and oxygen extraction ratios were low. As a result most patients had an arteriovenous oxygen content difference consistently less than  $2 \text{ ml} \cdot \text{dl}^{-1}$ . A possible source of error for  $\text{SvO}_2$

was aspiration of arterialised blood from the pulmonary artery catheter (i.e. oxygenated blood from pulmonary capillaries). However, I checked that the pulmonary artery pressure trace was unwedged prior to each sample and aspirated blood slowly which, in the presence of high pulmonary blood flows, made arterialisation unlikely. Blood oxygen content was calculated from measurements of haemoglobin oxygen saturation, oxygen tension, and haemoglobin concentration each of which has an associated measurement error. Inaccuracy attributable to storage and transport of samples and operator error was minimised by analysing them immediately. However, the accuracy of measurements was still limited by the precision of the cooximeter and blood gas analyser used. Errors in cooximeter measurements of oxygen saturation can be significant particularly for SvO<sub>2</sub> which lies on the steep part of the haemoglobin-oxygen dissociation curve (Woda et al 1996, Beards et al 1994). Errors associated with haemoglobin concentration measurements may also be significant particularly if sample mixing is incomplete. These errors are randomly propagated and multiplied in the calculation of arteriovenous oxygen content difference such that errors in the final calculation may be substantially greater than the sum of the measurement errors associated with each primary variable. This is likely to be particularly true when the arteriovenous oxygen content difference is small. In order to quantify the relative importance of this in VO<sub>2</sub>Fick calculations it is possible to derive a mathematical model as follows:

Suppose during a period of sampling the true arteriovenous oxygen content difference does not change, then it is a reasonable assumption that the mean of a large number of arteriovenous oxygen content difference calculations is the true value, and that measurement errors will result in a range of values around the mean which should be normally distributed. If, for simplicity, the contribution of PaO<sub>2</sub> and PvO<sub>2</sub> which are usually very small, are excluded the formula for arteriovenous oxygen content difference (AV difference) is:

$$\text{AV difference} = (1.34 \times \text{Hb} \times \text{SaO}_2) - (1.34 \times \text{Hb} \times \text{SvO}_2)$$

The errors in arterial and venous oxygen content can be subdivided on the assumption

that the errors in haemoglobin concentration and saturation measurement approximately summate.

$$\text{Thus:} \quad E_a \cdot A = [E_{Hb} + E_{Sa}] \cdot [Hb \cdot SaO_2 \cdot 1.34] \quad [\text{equation 1}]$$

$$E_v \cdot V = [E_{Hb} + E_{Sv}] \cdot [Hb \cdot SvO_2 \cdot 1.34] \quad [\text{equation 2}]$$

Where

$A$ : arterial oxygen content (ml.dl<sup>-1</sup>)

$V$ : venous oxygen content (ml.dl<sup>-1</sup>)

$E_a$ : maximum error in arterial oxygen content estimation (% , expressed as a fraction)

$E_v$ : maximum error in venous oxygen content estimation (% , expressed as a fraction)

$E_{Hb}$ : error in hemoglobin measurement (% , expressed as a fraction)

$E_{Sa}$ : error in  $SaO_2$  (% , expressed as a fraction)

$E_{Sv}$ : error in  $SvO_2$  (% , expressed as a fraction)

Errors in AV difference can be defined as:

$$E_{av} = E_a \cdot A + E_v \cdot V \quad [\text{equation 3}]$$

and

$$PE_{av} = \frac{E_{av}}{A - V} \cdot 100 \quad [\text{equation 4}]$$

Where  $E_{av}$  maximum absolute error in AV difference (ml.dl<sup>-1</sup>)

$PE_{av}$  maximum percent error in AV difference (%)

Combining equations 3 and 4 gives:

$$PE_{av} = \frac{E_a \cdot A + E_v \cdot V}{A - V} \cdot 100 \quad [\text{equation 5}]$$

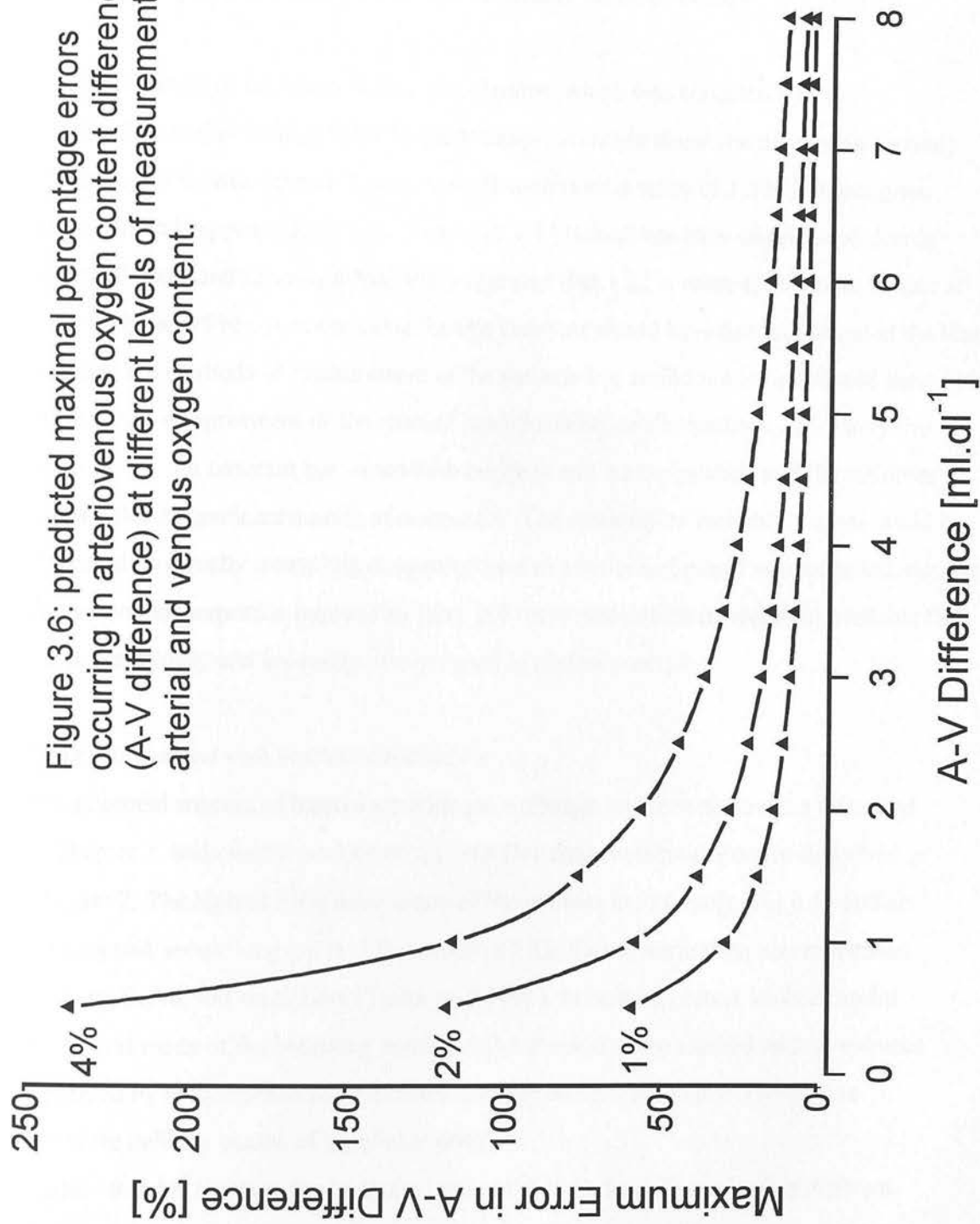
This equation predicts the maximum errors which could occur with different levels of measurement error. The probability of this degree of inaccuracy is very small but allows the *dispersion* of errors which are likely to occur at different arteriovenous oxygen content differences to be compared. These maximum errors are illustrated in figure 3.6. This figure indicates that as the true arteriovenous oxygen content difference becomes progressively smaller, or as the level of measurement error increases, so the chance of a single arteriovenous oxygen content difference calculation from clinical measurements being close to the true value decreases disproportionately. In clinical practice when the arteriovenous oxygen content difference is small the cardiac output is usually large which further magnifies the errors in the final calculation of oxygen consumption. This is well illustrated by an example:

Example 1: normal haemodynamic pattern.

	True Value	Measured Value	% Error
SaO <sub>2</sub> (%)	98	97	1.0
SvO <sub>2</sub> (%)	67	67.7	1.0
Hb (g.l <sup>-1</sup> )	12	12.3	2.5
Arterial O <sub>2</sub> content (ml.dl <sup>-1</sup> )	15.8	16.0	1.3
Venous O <sub>2</sub> content (ml.dl <sup>-1</sup> )	10.8	11.2	3.7
AV difference (ml.dl <sup>-1</sup> )	5.0	4.8	4.0
Cardiac Output (l.min <sup>-1</sup> )	5.0	4.7	6.0
VO <sub>2</sub> (ml.min <sup>-1</sup> )	250	226	9.6

Example 2: hyperdynamic pattern.

	True Value	Measured Value	% Error
SaO <sub>2</sub> (%)	98	97	1.0
SvO <sub>2</sub> (%)	85	85.9	1.0
Hb (g.l <sup>-1</sup> )	12	12.3	2.5
Arterial O <sub>2</sub> content (ml.dl <sup>-1</sup> )	15.8	16.0	1.3
Venous O <sub>2</sub> content (ml.dl <sup>-1</sup> )	13.7	14.2	3.6
AV difference (ml.dl <sup>-1</sup> )	2.1	1.8	14.3
Cardiac Output (l.min <sup>-1</sup> )	12	11.3	5.8
VO <sub>2</sub> (ml.min <sup>-1</sup> )	250	203	18.8





In both examples the true  $\text{VO}_2$  is identical and the size of the errors in haemoglobin concentration, arterial oxygen saturation, and mixed venous oxygen saturation are similar and typical of the accuracy of most cooximeters used in clinical practice. The pattern of random errors is the same in both cases (haemoglobin and  $\text{SvO}_2$  overestimated,  $\text{SaO}_2$  and cardiac output underestimated). Although individual measurement errors are similar, greater propagation with the hyperdynamic doubles the error in  $\text{VO}_2$ .

A further source of error in  $\text{VO}_2$ Fick calculations, which was considered in the introduction to this thesis, relates to the assumptions made about the combining capacity of haemoglobin with oxygen. Under optimal conditions a value of 1.39ml  $\text{O}_2$  per gram haemoglobin is appropriate, I used a value of 1.34 (which has been widely used during critical illness), and recently it has been suggested that 1.31 is more appropriate (Jolliet et al 1996, Nunn 1996). A lower value for this constant would have further increased the bias between the methods of measurement in the patients but would not have affected the width of the limits of agreement or the relative reproducibility of the methods. It is likely that the true value is not constant but varies both between and within patients at different times making this a significant source of inaccuracy. The accuracy of Fick calculations could be increased by directly measuring oxygen content in arterial and mixed venous blood, but the equipment and expertise required to carry out these measurements were not available for the present study and are rarely, if ever, used in clinical practice.

#### *Errors associated with indirect calorimetry.*

The potential sources of inaccuracy with gas exchange measurements were discussed in Chapter 1, and clinical performance of the Deltatrac metabolic monitor described in Chapter 2. The highest  $\text{FIO}_2$  used in any of the patients in this study was 0.55 and no patients had severe lung injury. Fluctuation in  $\text{FIO}_2$  during inspiration was minimised by using Servo 900 ventilators (Tissot et al 1995). In order to detect leaks a careful check was made of the breathing system, and a check that the expired minute volumes displayed by the Deltatrac and ventilator corresponded consistently. These were therefore unlikely causes of significant error.

Carbon dioxide stores in the body are large, exist in multiple forms, and in different

physiological compartments (Nunn 1977). These are normally in equilibrium but it may take 90 minutes after disruption of this steady state for equilibrium to be completely re-established although the majority of the process occurs within the first 20 minutes as might be expected with a multiexponential process (Henneberg et al 1987, Taskar et al 1995). During this time the accuracy of oxygen consumption measurements made with the Deltatrac may be reduced because gas exchange across the lungs is not identical to metabolic production by the body. In ventilated patients changes made to alveolar ventilation are the most common reason for disruption of the steady state but in the patients in this study ventilation was not changed unless clinically indicated and when this was necessary at least 1 hour was allowed to elapse before further data were collected. In addition patients were paralysed and sedated which eliminated spontaneous changes in minute ventilation and reduced spontaneous changes in oxygen consumption. Large changes in venous return and cardiac output may alter  $\text{VCO}_2$  and this could have influenced  $\text{VO}_2$  calorimetry in some of the patients (Shibutani et al 1994). However there were no major changes in  $\text{VCO}_2$  even during periods of haemodynamic change suggesting that this was not a major source of inaccuracy during Deltatrac recordings. A further factor which might have disrupted steady state was altered acid-base balance. If the acid-base status of patients altered rapidly over the study period, carbon dioxide generated as a result of buffering rather than oxidative metabolism could have reduced the validity of  $\text{VO}_2$  calorimetry. However, none of the patients received bicarbonate therapy during the study period, and hydrogen ion and standard bicarbonate concentrations did not alter significantly. I therefore consider it unlikely that this was a significant source of error.

### *Reproducibility*

The estimation of reproducibility indicated that  $\text{VO}_2\text{Fick}$  varied more because of measurement errors than  $\text{VO}_2$  calorimetry; the ratio of the WPSD of  $\text{VO}_2\text{Fick}$  relative to  $\text{VO}_2$  calorimetry being 2.1. This was consistent with most of the disagreement between the methods being attributable to  $\text{VO}_2\text{Fick}$ . The coefficients of variation for  $\text{VO}_2\text{Fick}$  in individual patients were also substantially larger than for  $\text{VO}_2$  calorimetry. It could be argued that these differences in reproducibility occurred because the

calorimeter was insufficiently sensitive to detect changes in oxygen consumption in response to altered delivery. However, Ronco and Phang (1991) showed that the Deltatrac metabolic monitor was able to accurately detect simulated changes in  $\text{VO}_2$  made using a lung model, even at higher inspired oxygen fractions than those used in the present study.

In a large mixed group of general intensive care patients Hanique et al (1994b) found the ratio of WPSDs of  $\text{VO}_2\text{Fick}$  to  $\text{VO}_2\text{calorimetry}$  was 1.4. The relative reproducibility of  $\text{VO}_2\text{Fick}$  may have been better in their study because the mean arteriovenous oxygen content difference was larger than in our patients, although they do not document a value for this. Bizouarn et al (1995) found the repeatability of both methods of measurement was similar in patients studied following cardiopulmonary bypass. In that study the mean arteriovenous oxygen content difference was  $4.1 \text{ ml.dl}^{-1}$ , mean cardiac output was much lower and, unlike patients in the present study, measurements were obtained during a period of complete cardiorespiratory stability. The limits of agreement in the present study were  $+19$  to  $-101 \text{ ml.min}^{-1}.\text{m}^{-2}$ , which are wider than for any other published comparison of  $\text{VO}_2\text{Fick}$  and  $\text{VO}_2\text{calorimetry}$ , indicating very poor agreement between the methods. In previous studies the limits of agreement have been reported as  $\pm 52 \text{ ml.min}^{-1}.\text{m}^{-2}$  (mixed general intensive care patients)(Hanique et al 1994b),  $+3$  to  $-33 \text{ ml.min}^{-1}.\text{m}^{-2}$  (post coronary artery bypass surgery)(Bizouarn et al 1995), and  $+27$  to  $-61.5 \text{ ml.min}^{-1}.\text{m}^{-2}$  (patients with severe sepsis)(Esen et al 1996). These data further indicate the influence of haemodynamic pattern and clinical conditions on the relative accuracy of the different methods of determining  $\text{VO}_2$  and support the conjecture that gas exchange methods are preferable in hyperdynamic patients.

In addition to measurement errors the methods may have given differing results because they were estimating different physiological parameters. Analysis of respiratory gases estimates whole body  $\text{VO}_2$  since gas exchange across non pulmonary surfaces is insignificant. In contrast Fick calculations utilize blood samples drawn from the pulmonary artery and a peripheral artery. Oxygen extracted from the

circulation between these points is therefore ignored. This may include pulmonary oxygen consumption since bronchial venous blood returns to the heart partly via the pulmonary veins. When data were pooled  $\text{VO}_2\text{Fick}$  was significantly less than  $\text{VO}_2\text{calorimetry}$ ; this was also the case in all but one of the patients when examined individually. Most previous studies in humans which have compared  $\text{VO}_2\text{Fick}$  with  $\text{VO}_2\text{calorimetry}$  have similar findings (Bizouarn et al 1995, Takala et al 1989, Jolliet et al 1996, Esen et al 1996, Oudemans-van Straaten et al 1993, Myburgh et al 1992, Smithies et al 1991, De Backer et al 1994). In a study in pigs  $\text{VO}_2\text{Fick}$  was less than  $\text{VO}_2$  measured by spirometry which is generally considered the “gold standard” for  $\text{VO}_2$  measurement (Stock and Ryan 1996) although, for reasons which are unclear, another similar study had opposite findings (Thrush 1996). A number of authors have suggested that the difference between measurements made with the techniques can be used to estimate pulmonary oxygen consumption (Jolliet et al 1996, Oudemans-van Straaten et al 1993, Light 1988). With this hypothesis Light (1988) demonstrated that pulmonary oxygen consumption increased during experimental pneumonia in dogs. More recently, Jolliet et al (1996) used this method to estimate pulmonary oxygen consumption in patients with ARDS. In the present study a systematic bias was found between the two methods of measurement, but this varied widely both within and between patients. A possible explanation for this observation was that pulmonary oxygen consumption was significant and varied over the 5 hour study period. However, this was an unlikely reason for the wide range of bias observed within patients because none had severe lung injury (in all cases lung injury score according to Murray et al (1988) was  $\leq 1$ ) or evidence of pneumonia at the time of the study, and in most gas exchange did not alter significantly during the study period. Variability in bias was also random during the study period which was not in keeping with an ongoing pulmonary inflammatory process. The magnitude of the median bias observed in some patients represented 50% of whole body  $\text{VO}_2$  measured by indirect calorimetry which seemed unlikely to be attributable to pulmonary oxygen consumption alone. The data most likely indicate that the measurement errors associated with this method of estimating pulmonary oxygen consumption are large and the clinical validity low, at least in patients with hyperdynamic circulations. The

repeatability of pulmonary oxygen consumption calculated in this way has not been estimated in published studies.

### *Mathematical coupling*

When the  $\text{VO}_2\text{Fick}$  data were used the slopes of the  $\text{DO}_2/\text{VO}_2$  relationships were greater than if the  $\text{VO}_2\text{calorimetry}$  data were used. This was particularly the case when data from only the first hour of the study were used. Because  $\text{VO}_2\text{Fick}$  data were less reproducible, the spread of data around the regression slopes was much greater than with  $\text{VO}_2\text{calorimetry}$ . The likely explanation for the discrepancy between the methods of measurement is mathematical coupling. Taken alone the  $\text{VO}_2\text{Fick}$  data indicated significant supply dependency in most patients, particularly if confidence interval for the slopes were not considered. Harrison and colleagues (1991) pooled data and compared 2 data points during the first hour of N-acetylcysteine administration. With respect to time the data from the present study indicated that the discrepancy between  $\text{VO}_2\text{Fick}$  and  $\text{VO}_2\text{calorimetry}$  was greatest during this first hour which, as will be described in the second section of this chapter, was the period during which most alteration in cardiac output occurred. The classic description of how mathematical coupling causes an artificial positive relationship between oxygen delivery and consumption was made by Archie (1980). Archie used a random number generator to produce simulated random data for cardiac output and arteriovenous oxygen content difference and plotted the data against one another, which generated a random scattergraph (figure 3.7). However, when the product of each data pair was calculated, in the same way real data are used to calculate oxygen consumption using the reverse Fick method, re-plotted data for cardiac output and  $\text{VO}_2\text{Fick}$  were no longer random, but generated a significant positive relationship with a product moment correlation coefficient close to 0.7. This phenomenon occurs because of mathematical coupling and is closely analogous to plotting an oxygen delivery/consumption relationship in critically ill patients using the reverse Fick method. What has remained unclear in the critical care literature is whether this effect explains completely the apparent pathological supply dependency frequently documented in critically ill patients.



There are problems with the explanation of mathematical coupling put forward by Archie (1980) as it stands. In practice patients are not “random number generators” and cardiac output and arteriovenous oxygen content difference are physiologically coupled. Thus, under conditions of constant  $\text{VO}_2$ , as cardiac output and oxygen delivery increase so less tissue should be extracted by the tissues per volume of blood delivered and the arteriovenous oxygen content difference should decrease. However, there are 2 mechanisms whereby  $\text{DO}_2/\text{VO}_2$  data may tend to behave like random numbers:

*Pooling of data:* If data from more than one patient are superimposed and plotted together and then the relationship analysed, there is a strong tendency for the result to be a positive correlation. The relationship between the variables in individual patients may be obscured such that the conclusions drawn from the pooled data are different from the true relationships in individuals. This is likely for oxygen kinetics data because patients with low oxygen consumption tend to have low oxygen delivery and patients with high oxygen consumption tend to have high oxygen delivery. This is not a pathological phenomenon but simply the normal physiological matching between demand and supply (Weissman et al 1984, 1991, Boyd et al 1992).

*Large measurement errors:* The reverse Fick method should accurately determine oxygen consumption by the body (with the possible exception of the lungs as described previously) as long as all the measurements made are completely accurate. In practice this is never the case because all clinical measurements have an associated measurement error. I have clearly shown in this study that measurement errors associated with  $\text{VO}_2\text{Fick}$  measurements were large in the patients with fulminant hepatic failure, and investigated the reasons for this using a simple mathematical model. As the amount of measurement error increases, so data describing variables



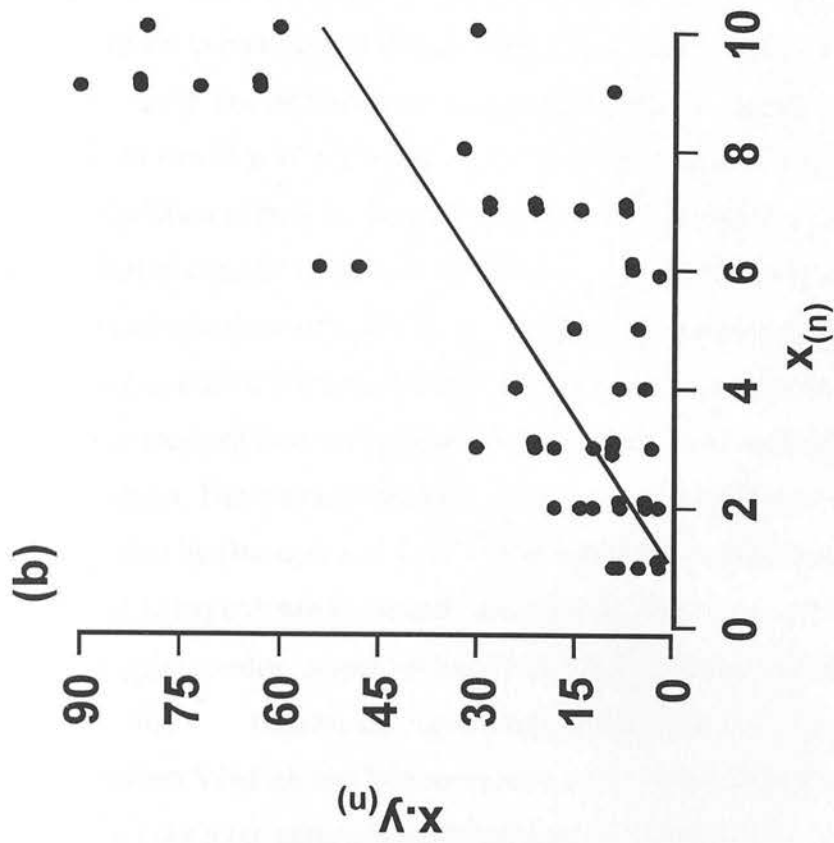
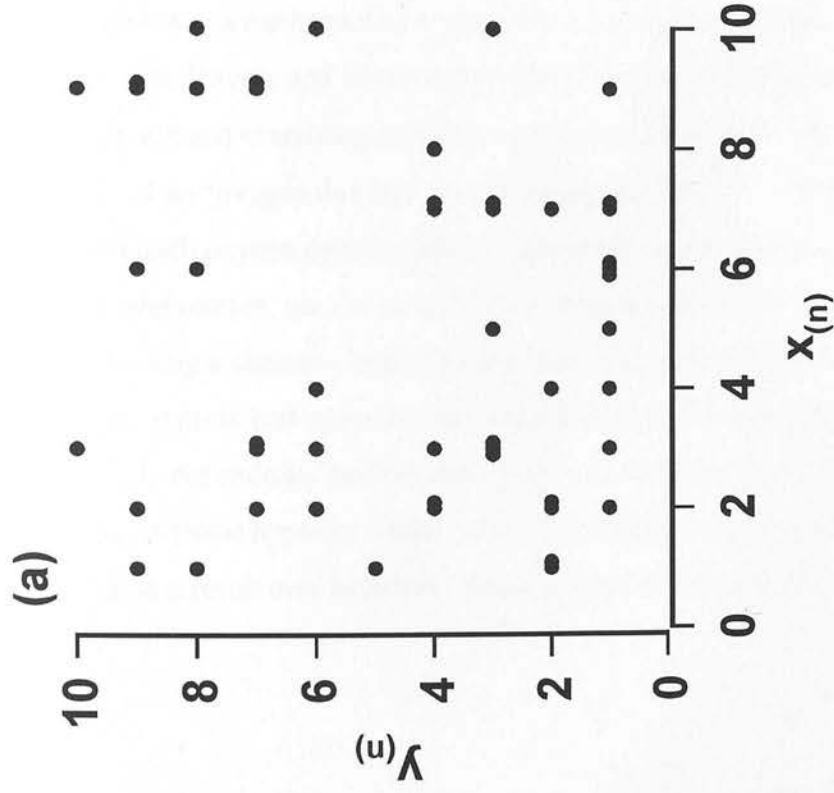


Figure 3.7: The effect of mathematical coupling of shared variables on a relationship illustrated using random numbers. In (a) 50 pairs of random numbers,  $x(n)$  and  $y(n)$ , between 1 and 10 are plotted producing a random scattergraph. In (b), a third variable,  $x \cdot y(n)$  the product of  $x(n)$  and  $y(n)$ , is plotted against  $x(n)$ . Despite the use of random numbers a positive correlation ( $r=0.7$ ) occurs because of mathematical coupling of the values of  $x(n)$ . (Modified from Archie, 1980)

which are physiologically linked, such as cardiac output and arteriovenous oxygen content difference, will behave increasing like random data such that the confounding effect of mathematical coupling becomes stronger. In the present study the technology used for cardiac output measurement should have resulted in a high degree of accuracy, and published work suggests that the repeatability of this technique is good (Bizouarn et al 1995). I have hypothesised that much of the error lies in the calculation of arteriovenous oxygen content difference because this difference was small in virtually all patients. If this were the case the effect of mathematical coupling in *individual* patients should be greatest during the period of greatest change in cardiac output because, in effect,  $VO_2\text{Fick}$  mirrors cardiac output. In the 11 patients who received N-acetylcysteine cardiac output varied most during the first hour of the infusion. This was also the same period after starting N-acetylcysteine that was studied by Harrison et al (1991). The data in the present study confirm the hypothesis that, in hyperdynamic patients, the effect of coupling is greatest during periods of changing cardiac output because  $DO_2/VO_2\text{Fick}$  slopes were significantly greater for the first hour than for the whole study period. This also explains why the discrepancy between  $VO_2\text{Fick}$  and  $VO_2\text{calorimetry}$  with respect to time was greatest during the first hour after starting N-acetylcysteine administration.

A third mechanism whereby mathematical coupling might cause a positive correlation which was a mathematical artefact relates to studies in which the relationship between oxygen delivery and consumption was studied by inducing an increase in oxygen delivery and examining its effect on oxygen consumption. An example of this was the use of an “oxygen flux test” to reveal oxygen debt (Vincent et al 1990). With this approach oxygen delivery and oxygen consumption were calculated before and after an intervention, usually an infusion of dobutamine, which increased cardiac output. If following a clinically significant increase in oxygen delivery an increase in oxygen consumption had occurred, this was considered indicative of pathological oxygen supply dependency and the need to maintain a higher level of oxygen delivery to reduce tissue hypoxia. These studies generally chose a positive change as an endpoint and as a result may have been biased toward selecting positive measurement errors, ie.

over-estimations of cardiac output. As any error in cardiac output is transmitted to  $VO_2$ Fick this causes systematic overestimation of  $VO_2$ . The net result is an impression that  $DO_2$  and  $VO_2$  are positively correlated variables whereas in fact the relationship may be wholly artificial. As a specific change in  $DO_2$  or cardiac output was not targetted in the present study this mechanism of mathematical coupling was not relevant.

## Conclusions

- 1) The agreement between the reverse Fick method and indirect calorimetry for determining oxygen consumption in patients with fulminant hepatic failure is very poor.
- 2) There is a systematic bias between the methods of measurement whereby oxygen consumption calculated using the reverse Fick method is less than that measured by indirect calorimetry. This bias is highly variable within and between patients.
- 3) The poor agreement between the methods is mostly attributable to the inaccuracies associated with the reverse Fick method. This is most likely explained by the propagation of measurement errors in patients with a hyperdynamic haemodynamic pattern combined with a small arteriovenous oxygen content difference.
- 4) When measurement errors are large the potential for mathematical coupling error, when examining the relationship between oxygen delivery and consumption using the reverse Fick method, is great.
- 5) The findings of Harrison and colleagues that N-acetylcysteine increases  $VO_2$  in patients with fulminant hepatic failure was probably an artifact caused by mathematical coupling.

## PART 2

### The effect of N-acetylcysteine on oxygen transport and uptake in patients with fulminant hepatic failure

#### Data

In view of the findings discussed in the first part of this chapter indirect calorimetry measurements of oxygen consumption were used for analysis.

#### *Analysis of Data*

*Effect of N-acetylcysteine on haemodynamic variables:* The mean cardiac index, mean arterial pressure, and systemic vascular resistance index were calculated for a 10 minute period at baseline minus 30 minutes, baseline, and each hour for 5 hours after starting N-acetylcysteine or placebo infusions. Pulmonary artery wedge pressure was measured every 30 minutes.

*Effect of N-acetylcysteine on  $VO_2$  and OER:* In each patient who received N-acetylcysteine the 6 data pairs were used to construct a  $DO_2/VO_2$  relationship, and linear regression analysis was used to calculate the slope of each line. The relationship was considered significant if the slope was significantly different from zero at the  $P < 0.05$  level. The same method of analysis was used to examine the relationship between  $DO_2$  and the OER. Changes in  $VO_2$  and OER from baseline in relation to time were plotted for both the N-acetylcysteine and placebo groups.

*Effect of N-acetylcysteine on indirect markers of tissue hypoxia:* Changes in base excess and whole blood lactate from baseline in relation to time were plotted for each patient.

*Relationship between plasma N-acetylcysteine levels and haemodynamic changes:* For patients who received N-acetylcysteine, the relationship between the peak (30 minutes) and plateau (300 minutes) plasma N-acetylcysteine concentrations and

changes in haemodynamic variables from baseline were examined by calculating the Pearson product moment correlation coefficients.

*Statistical analysis:* Changes in haemodynamic variables,  $\text{DO}_2$ ,  $\text{VO}_2$ , OER, base excess, and whole blood lactate concentrations over the study period were compared with baseline values within each group. Changes for these variables were compared between the N-acetylcysteine and placebo groups by calculating the area under the curve (AUC) for each patient in relation to time for the 5 hours of the study. Each hour of the study period and the incremental AUCs were compared. Non parametric tests were used applying Bonferroni's correction for multiple significance tests as appropriate.  $P < 0.05$  was considered statistically significant.

## Results

Baseline data indicated that patients were haemodynamically stable prior to receiving the N-acetylcysteine or placebo infusions (table 3.6). Pulmonary artery blood temperature did not alter significantly in either group over the study period (N-acetylcysteine group: baseline mean (sd)  $36.4^\circ\text{C}$  (0.6), 5 hours  $36.8^\circ\text{C}$  (1.1); placebo baseline  $36.5^\circ\text{C}$  (0.5), 5 hours  $36.4^\circ\text{C}$  (0.5)).

*Haemodynamic changes.* Patients exhibited a variable response to N-acetylcysteine and there were clear responders and non-responders within the group (figures 3.8 and 3.9). Overall, in comparison to baseline no statistically significant changes in cardiac index occurred over the study period either within the N-acetylcysteine or placebo groups. Comparison of AUCs between the groups indicated a trend towards an increase in cardiac output over the first 4 hours after starting N-acetylcysteine (figure 3.8). However, this trend was not statistically significant for any individual hour of the study or comparing incremental AUCs. Mean arterial pressure did not change significantly from baseline at any time point over the study period in either group and AUC analysis revealed no differences between the groups. Systemic vascular

resistance index decreased at 60 minutes in comparison to baseline in the N-acetylcysteine group, but AUC analysis revealed no differences from the placebo group at any time point (figure 3.9). The mean pulmonary artery wedge pressure was slightly lower in the placebo group but this was not statistically significant and values remained constant over the study period (figure 3.9).

*Effect of N-acetylcysteine on  $\dot{V}O_2$  and oxygen extraction.* The  $\dot{D}O_2/\dot{V}O_2$  relationship for each patient who received N-acetylcysteine is illustrated in figure 3.10 and summarised in table 3.7. Delivery-dependent oxygen consumption, defined as a slope which was significantly different from zero, was present in only 3 patients. There was no relationship between the slope of the  $\dot{D}O_2/\dot{V}O_2$  relationship and either the baseline lactate concentration or base excess (table 3.7). There was no difference between patients receiving noradrenaline or prostacyclin during the study period and those who did not, although numbers for comparison were small. Oxygen extraction ratio was low in the patients and changes in response to altered oxygen delivery were small. Despite this, in 10 patients the OER decreased significantly as oxygen delivery increased (figure 3.11 and table 3.7).

In relation to time a statistically significant, but clinically insignificant increase in oxygen consumption occurred in comparison with baseline values in the N-acetylcysteine group at 30 minutes (median increase  $7 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ,  $P < 0.05$ ) and at 60 minutes (median increase  $7 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ,  $P < 0.05$ ) (figure 3.12). There were no significant changes in oxygen consumption in comparison to baseline values in the placebo group. AUC comparison between the groups demonstrated no significant differences for any hour of the study or comparing incremental AUCs. There was a trend for  $\dot{D}O_2$  to increase in the N-acetylcysteine group both in relation to baseline and in comparison to the placebo group (figure 3.12). These changes were related to changes in cardiac output, and as with cardiac output, were not statistically significant. OER, base excess, and whole blood lactate concentrations did not change significantly over the study period either in relation to baseline values or in comparison with the placebo group (figures 3.12 and 3.13).



TABLE 3.5: Baseline data. All values are median (1<sup>st</sup>, 3<sup>rd</sup> quartile). No significant differences between the two baseline values for either group of patients. No significant differences between the N-acetylcysteine and placebo groups at time zero.

	N-acetyl cysteine group		Placebo group	
	Zero minus 30 minutes	Zero	Zero minus 30 minutes	Zero
VO <sub>2</sub> I (ml.min <sup>-1</sup> .m <sup>-2</sup> )	130 (121, 146)	136 (121, 144)	126 (113, 147)	124 (110, 143)
Respiratory Quotient	0.84 (0.78, 0.91)	0.85 (0.78, 0.88)	0.77 (0.76, 0.80)	0.77 (0.76, 0.80)
VCO <sub>2</sub> I (ml.min <sup>-1</sup> .m <sup>-2</sup> )	106 (99, 118)	105 (99, 115)	103 (92, 108)	103 (90, 108)
Cardiac Index (l.min <sup>-1</sup> .m <sup>-2</sup> )	5.8 (4.4, 6.5)	5.1 (4.3, 6.7)	5.0 (4.0, 5.4)	4.9 (4.0, 5.4)
MAP (mmHg)	84 (73, 90)	81 (72, 89)	91 (75, 96)	84 (80, 90)
SVRI (dyne.sec.cm <sup>-5</sup> .m <sup>-2</sup> )	929 (726, 1432)	914 (787, 1449)	1333 (1143, 1620)	1502 (1115, 1650)

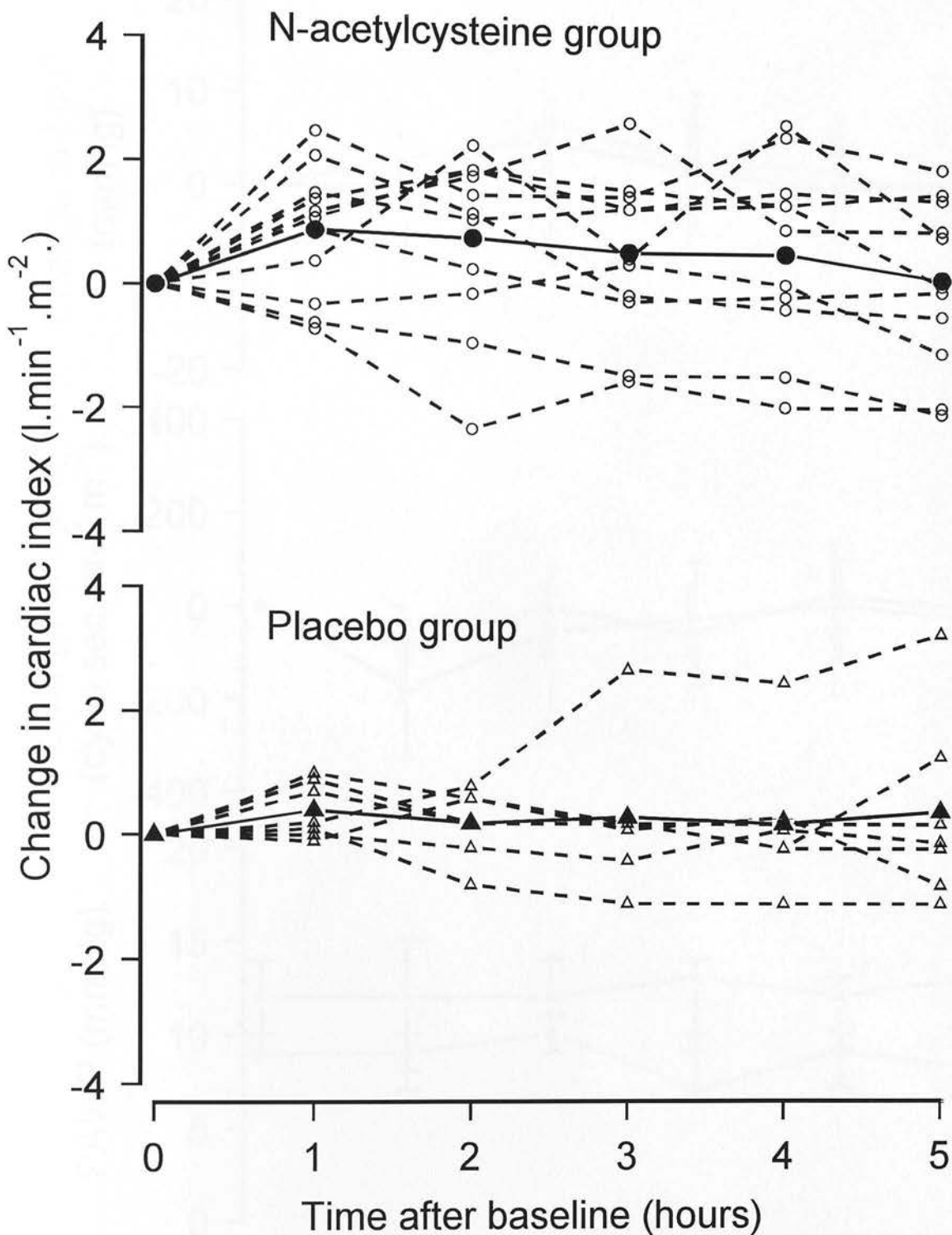


Figure 3.8: Values for cardiac index over the study period for each patient with relation to time.  
 Individual patient data shown in interrupted lines.  
 Mean group data solid lines. No significant differences between or within the groups

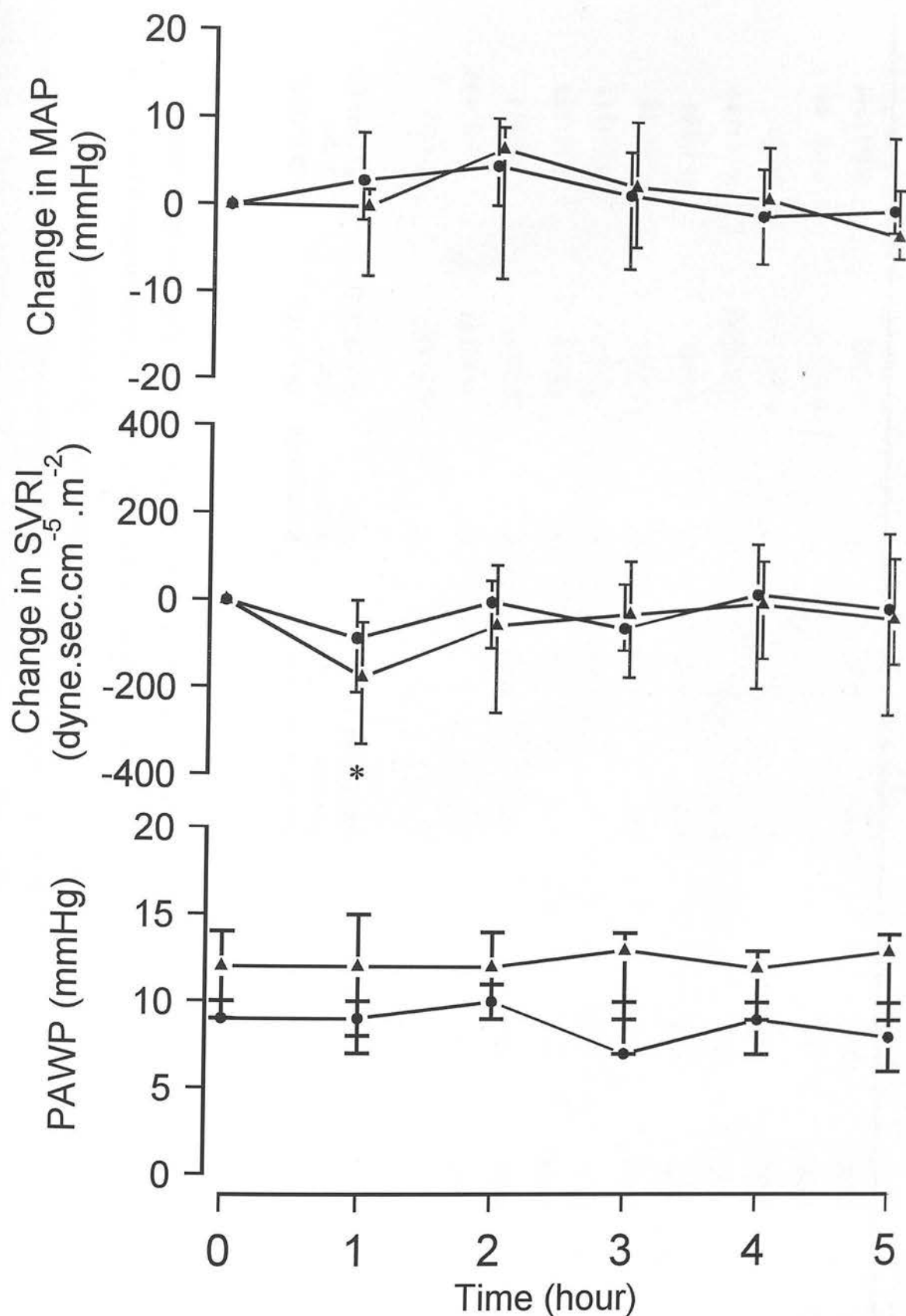


Figure 3.9: Changes in mean arterial pressure (MAP) and systemic vascular resistance index (SVRI), and pulmonary artery wedge pressure (PAWP) for the two groups. Triangles N-acetylcysteine, circles control groups. All values median (interquartile range). \* P<0.05 within N-acetylcysteine group compared to baseline.

TABLE 3.7: Summary of the relationship between  $\text{DO}_2$ ,  $\text{VO}_2$ , OER, and baseline whole blood lactate concentration, base excess, norepinephrine requirement and prostacyclin usage in patients who received N-acetylcysteine infusion. Patients receiving prostacyclin were undergoing continuous venovenous hemofiltration throughout the study period. Significance of the difference of the slopes from 0: †  $P<0.05$ ; ††  $P<0.01$ ; †††  $P<0.001$ .

Patient	Baseline lactate mmol.l <sup>-1</sup>	Baseline Values: Base excess mmol.l <sup>-1</sup>	Noradrenaline dose Baseline µg.kg <sup>-1</sup> .min <sup>-1</sup>	5 hours	Prostacyclin infusion Y/N	$\text{DO}_2/\text{VO}_2$ slope % (±95 CI)	$\text{DO}_2/\text{OER}$ slope % (±95 CI)
1	1.88	0.7	0	0	N	2 (±15)	-2 (±2)
2	1.35	5.5	0	0	Y	5 (±2) ††	-1 (0) †††
3	6.49	-11.6	0.10	0.12	Y	2 (±18)	-2 (±2) †
4	15.40	-8.5	1.60	1.95	Y	1 (±6)	-3 (±1) ††
5	6.20	-8.7	0.35	0.66	Y	-2 (±11)	-3 (±1) ††
6	8.60	-13.0	0.06	0.06	Y	2 (±6)	-1 (0) ††
7	5.70	-9.8	0.05	0.05	N	0 (±4)	-1 (0) ††
8	1.57	9.7	0	0	N	13 (±8) ††	-3 (±1) ††
9	3.36	-8.1	0	0	Y	9 (±17)	0 (±2)
10	2.38	-3.4	0	0	Y	3 (±2) †	-1 (0) ††
11	3.68	2.8	0.21	0.29	Y	-1 (±8)	-3 (±1) †††

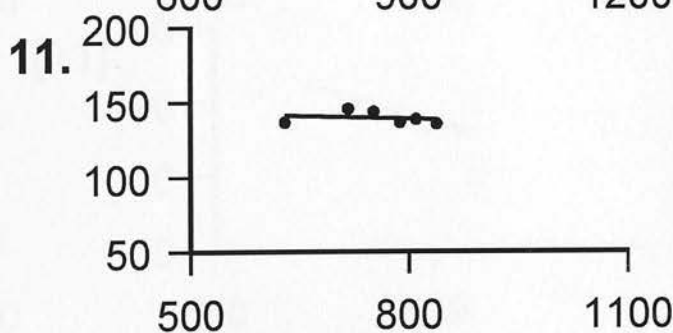
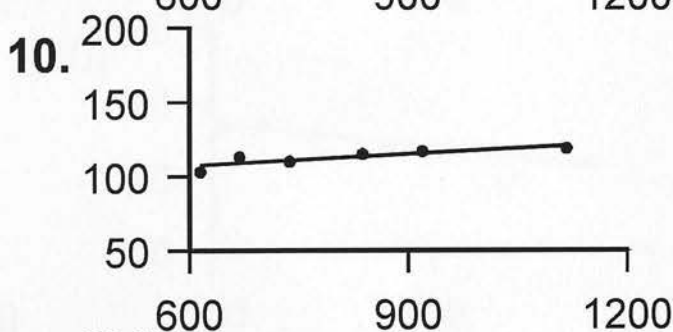
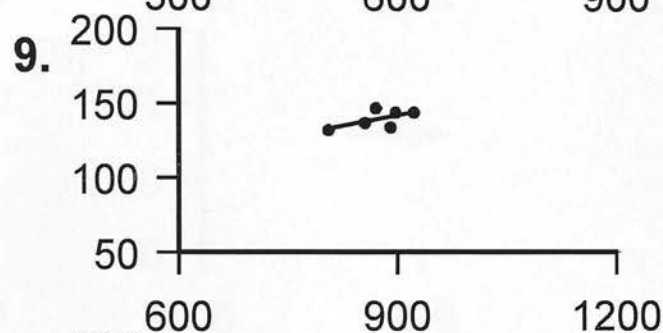
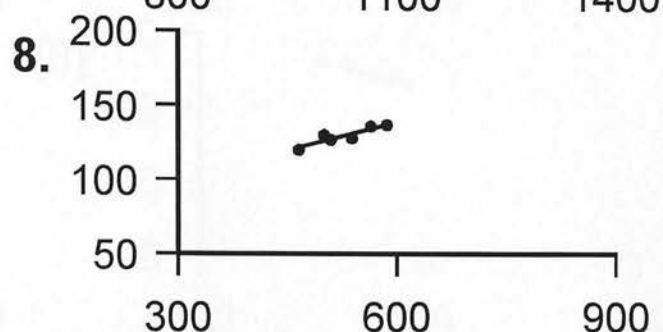
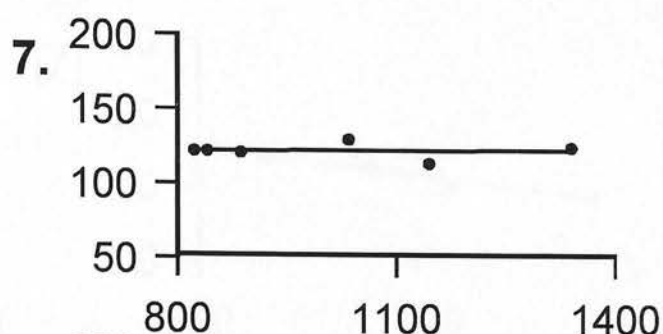
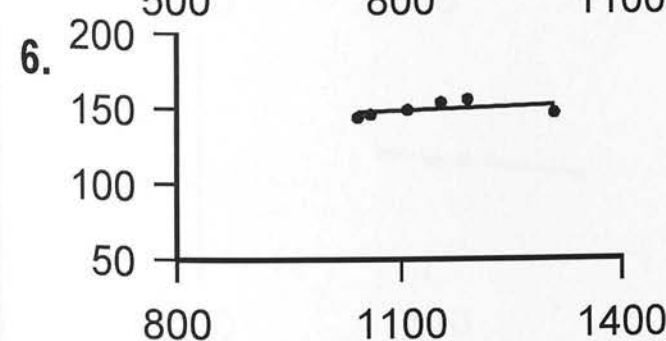
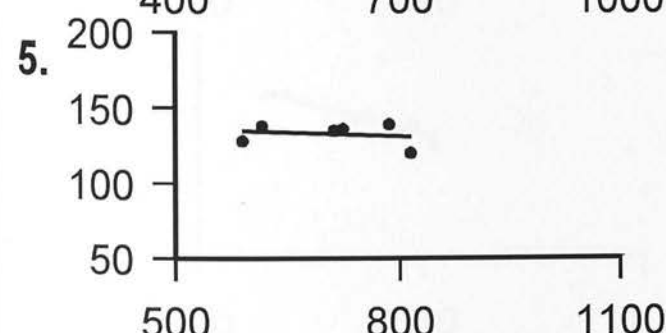
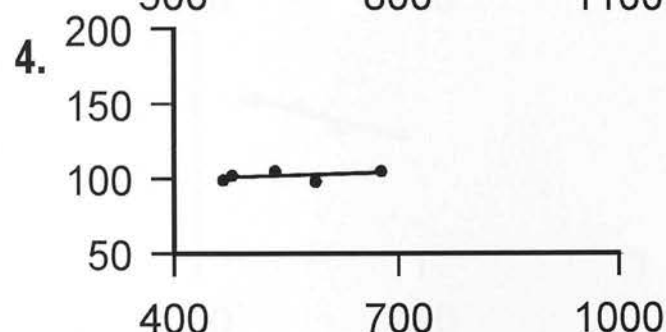
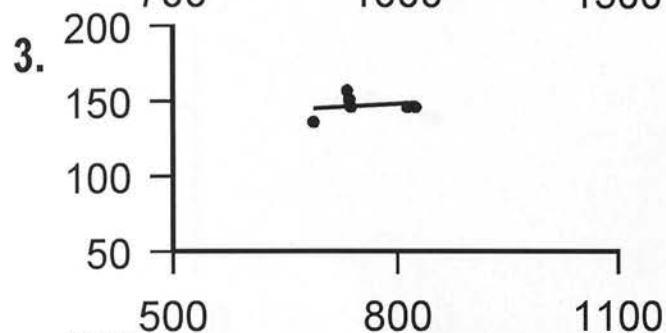
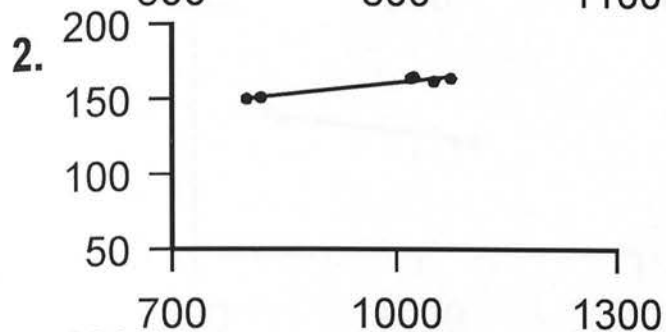
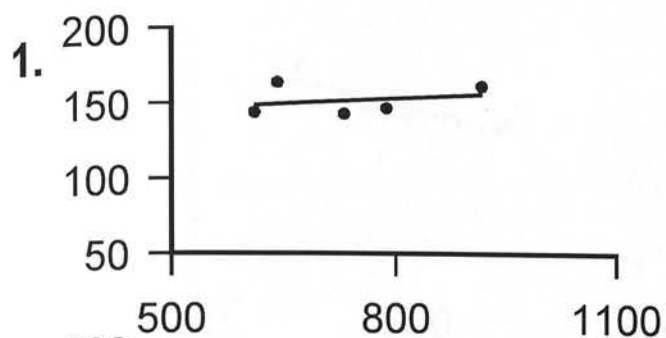


Figure 3.10:  
Relationship between oxygen delivery index (x-axis, ml.min<sup>-1</sup>.m<sup>-2</sup>) and oxygen consumption index (y-axis, ml.min<sup>-1</sup>.m<sup>-2</sup>) for each patient who received N-acetylcysteine.

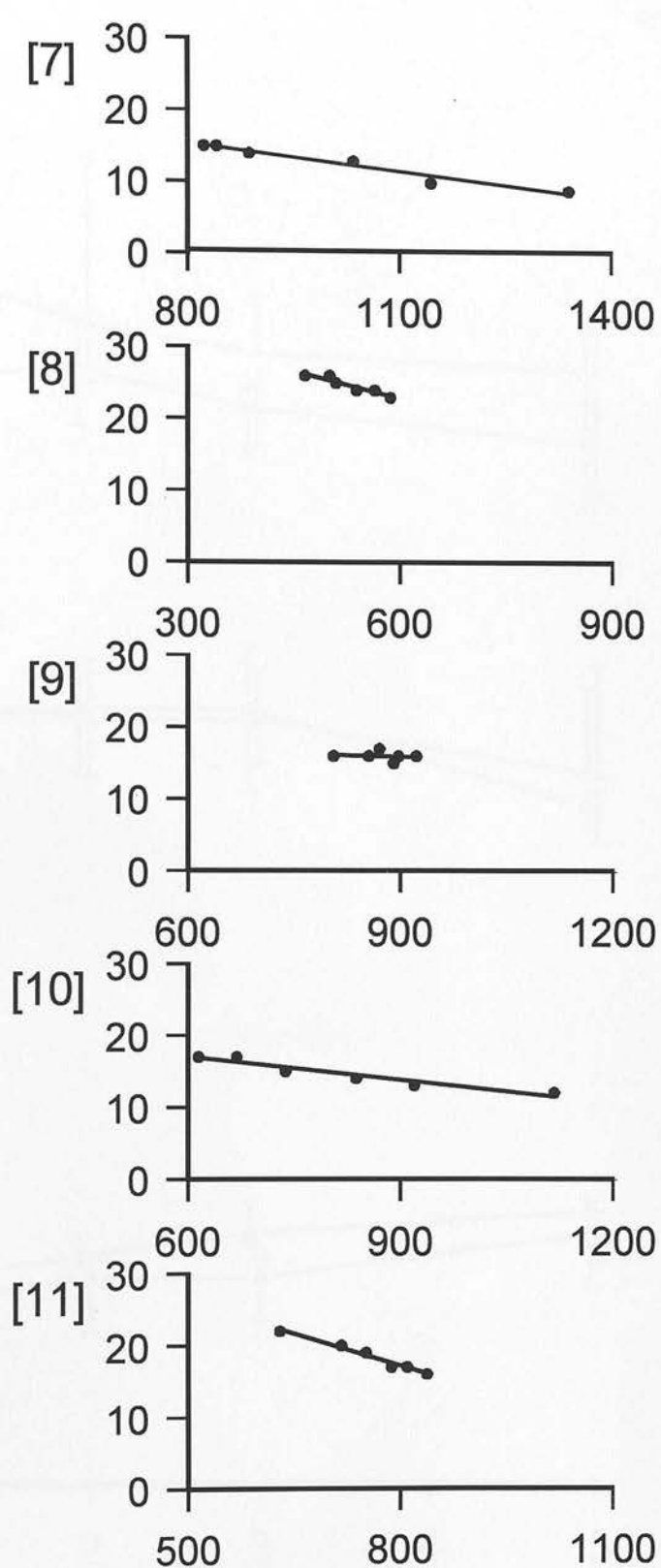
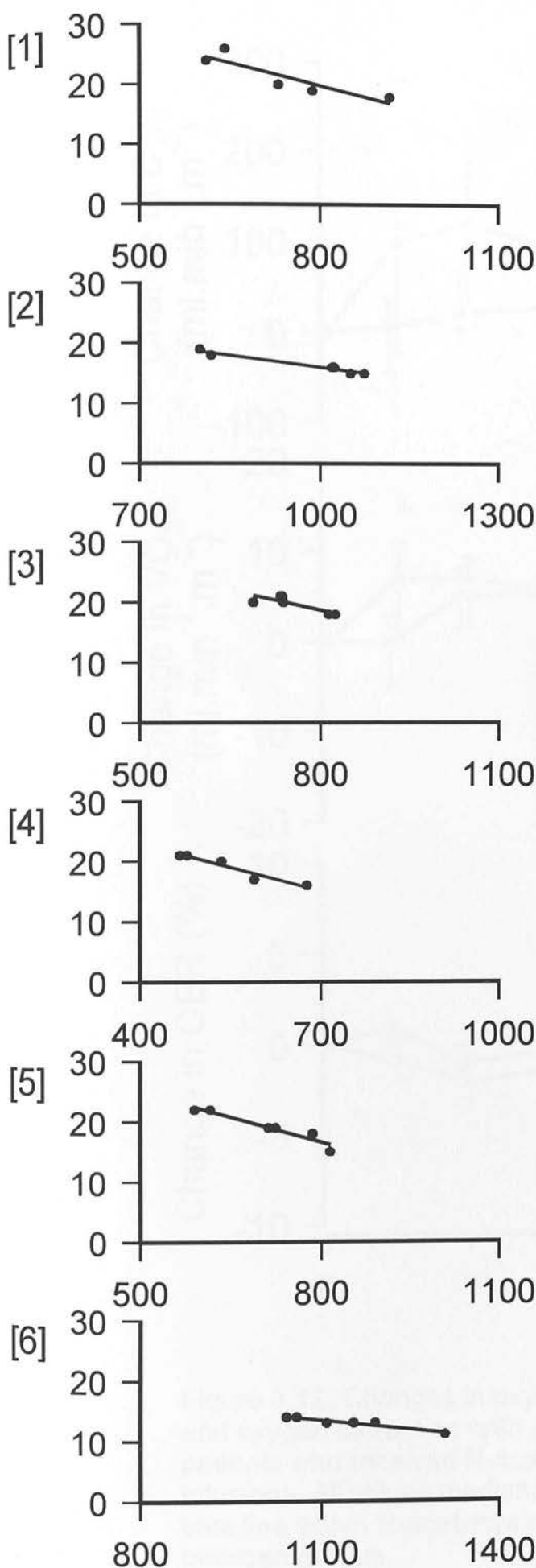


Figure 3.11:  
Relationship between oxygen delivery index (x-axis,  $\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ) and oxygen extraction ratio (y-axis, %) for each patient who received N-acetylcysteine.



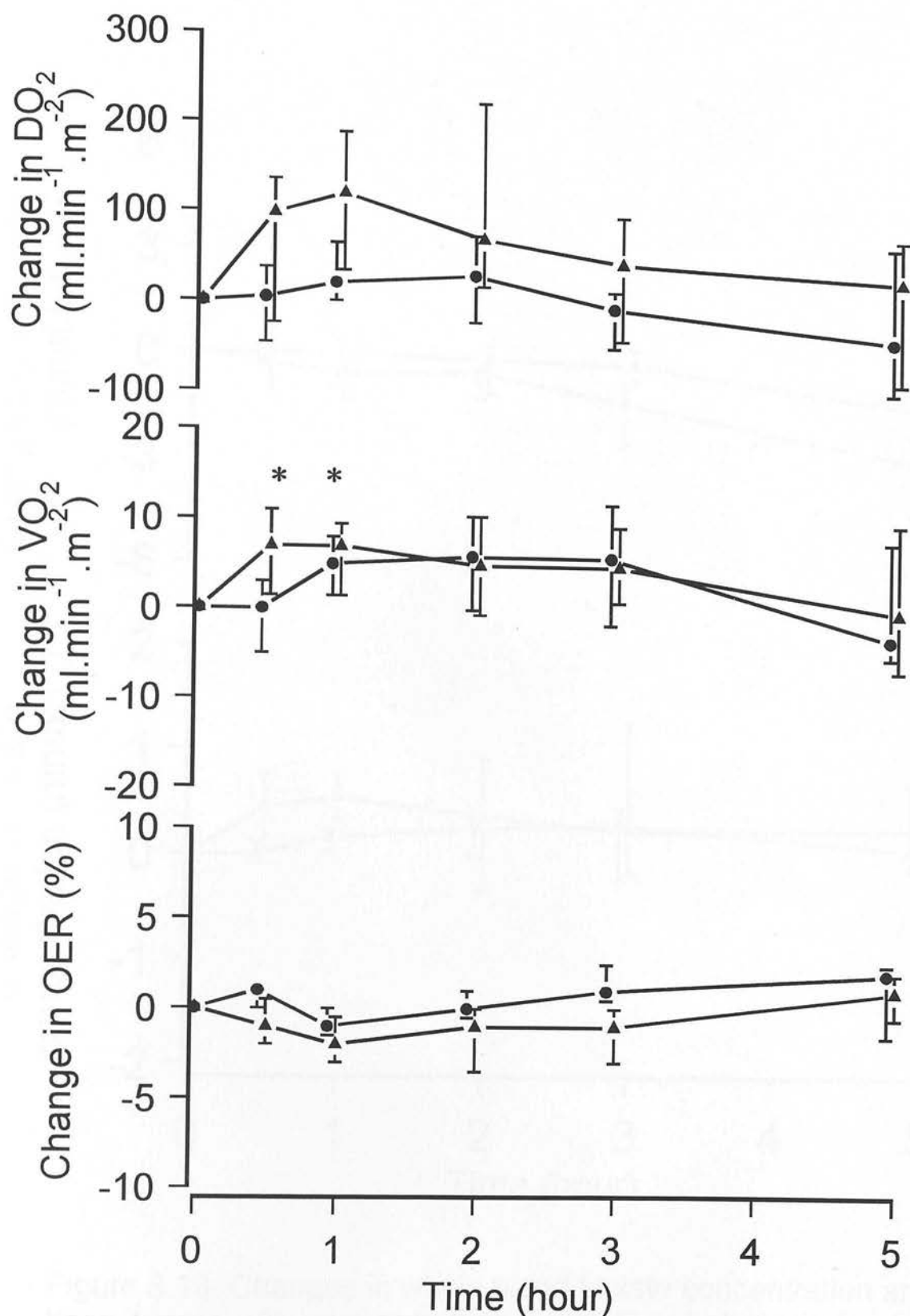


Figure 3.12: Changes in oxygen delivery ( $DO_2$ ), oxygen consumption ( $VO_2$ ) and oxygen extraction ratio (OER) with respect to time in the patients who received N-acetylcysteine (triangles) and placebo (circles) infusions. All values medians (interquartile ranges). \*  $p < 0.05$  compared to baseline within N-acetylcysteine group. No significant differences between groups

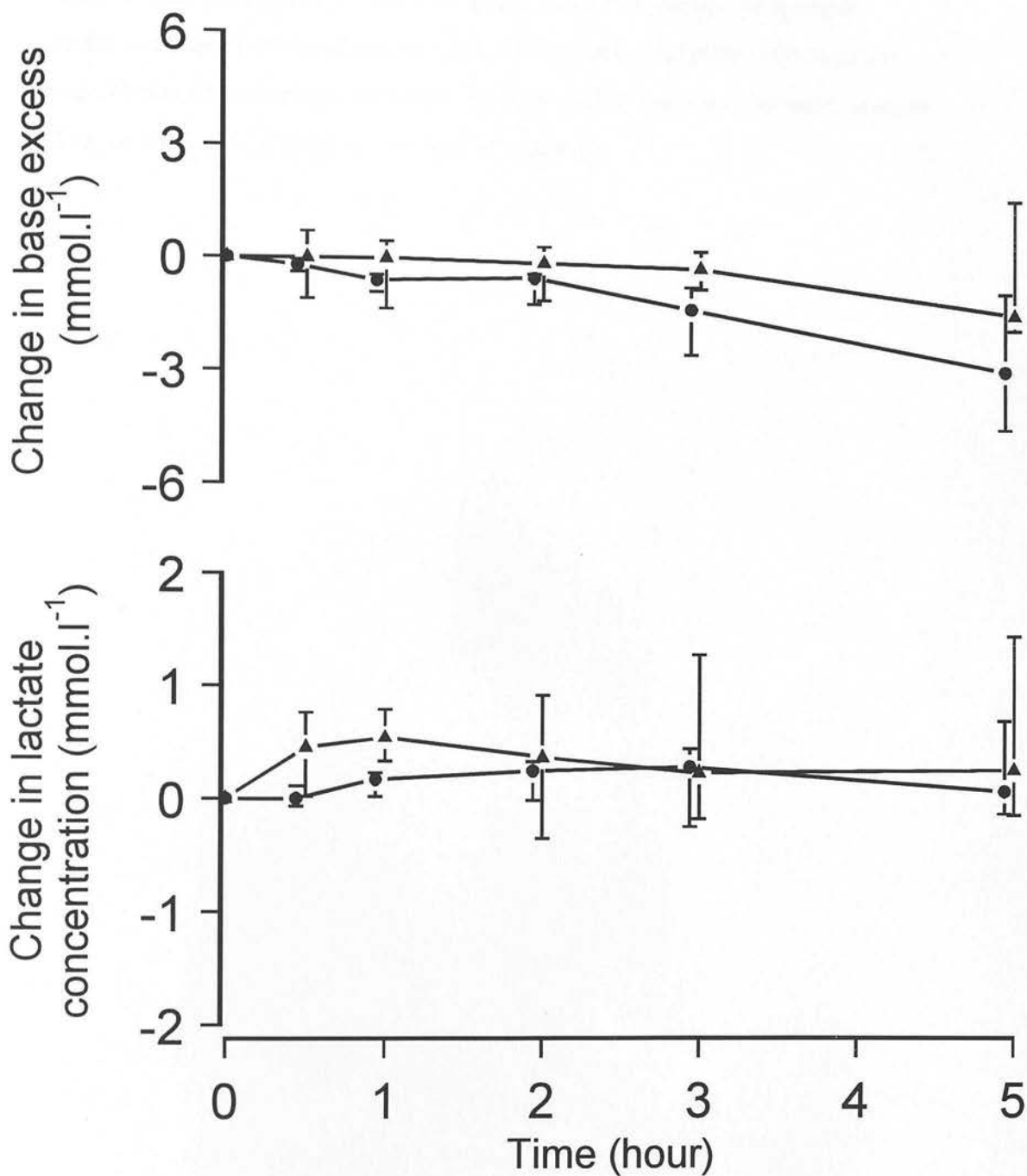
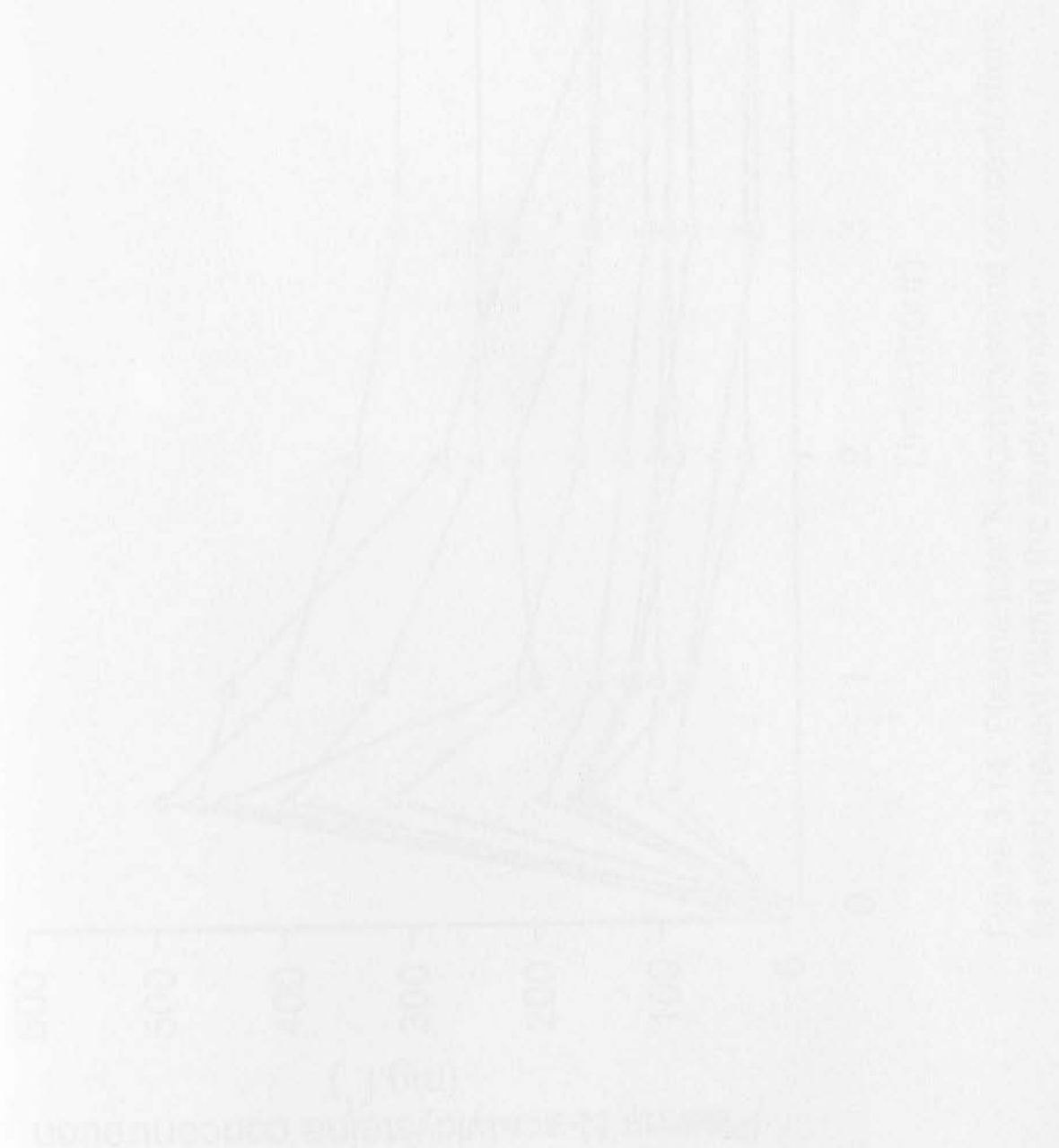


Figure 3.13: Changes in whole blood lactate concentration and base excess with relation to time during the study period. No significant differences between the groups. Triangles N-acetylcysteine group; circles control group. All values median (interquartile range)

*Plasma N-acetylcysteine concentrations.* N-acetylcysteine concentrations over the study period for each of the 11 patients are illustrated in figure 3.14. No correlations existed between changes in mean arterial pressure, cardiac output, or systemic vascular resistance from baseline, and peak (30 minutes) or plateau (300 minutes) plasma N-acetylcysteine concentrations. No relationship was found between changes in  $VO_2$  or OER and N-acetylcysteine concentrations.



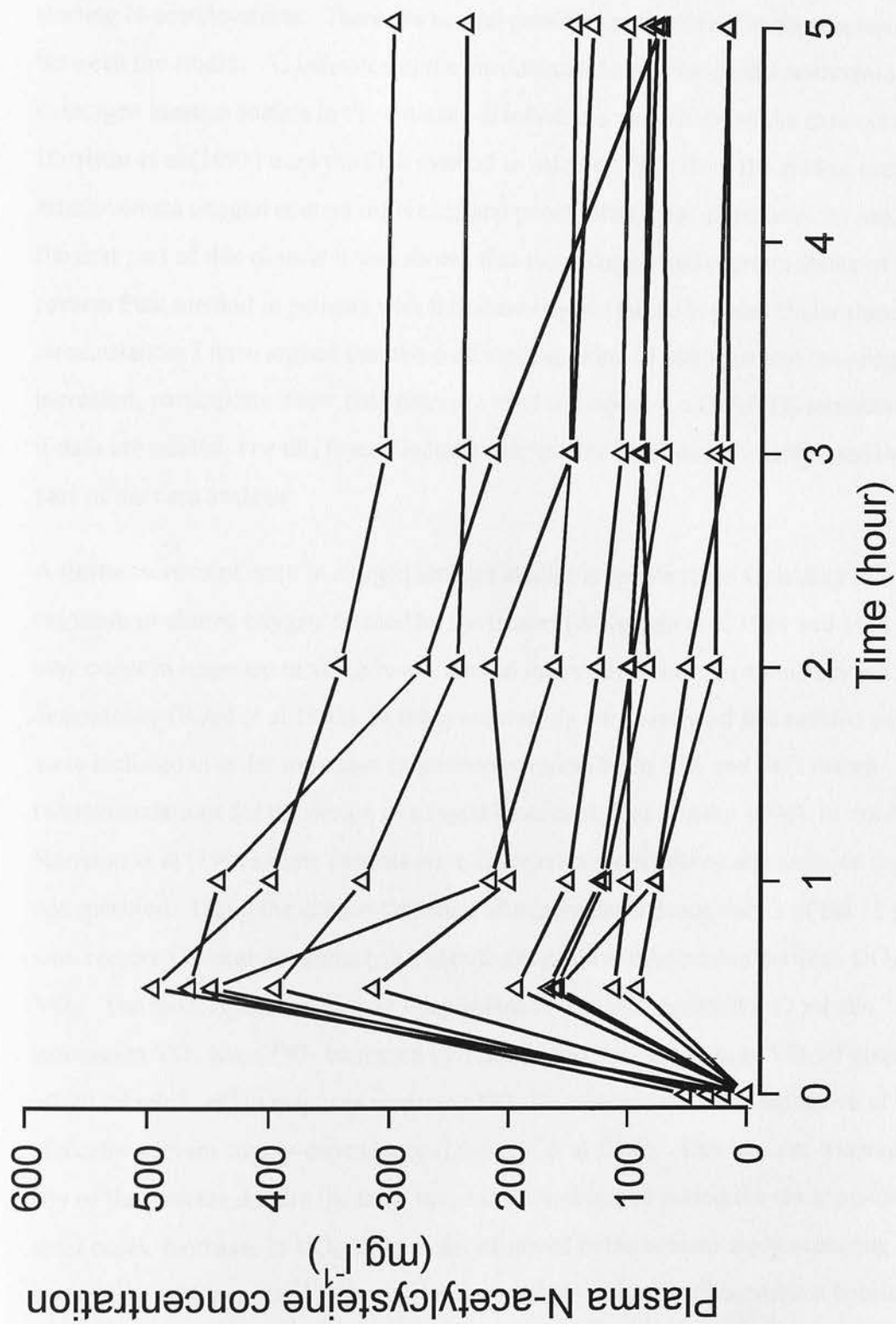


Figure 3.14: Plasma total N-acetylcysteine concentrations for each patient during the study period.

## Discussion

The results of this study differ markedly from those of Harrison et al (1991) who observed a mean increase in  $\text{VO}_2$  calculated by the Fick method of 46% 30 minutes after starting N-acetylcysteine. There are several possible explanations for the discrepancy between the studies. As indicated in the introduction to this thesis, the methodology used in oxygen kinetics studies in the critically ill influences the validity of the data obtained. Harrison et al (1991) used the Fick method to calculate  $\text{VO}_2$  from the cardiac output and arteriovenous oxygen content difference and pooled data from all patients for analysis. In the first part of this chapter it was shown that the accuracy and reproducibility of the reverse Fick method in patients with fulminant hepatic failure is poor. Under these circumstances I have argued that the confounding effect of mathematical coupling is increased, particularly if few data pairs are used to construct a  $\text{DO}_2/\text{VO}_2$  relationship and if data are pooled. For this reason indirect calorimetry data were primarily used in this part of the data analysis.

A further source of error in oxygen kinetics studies is spontaneous variability in  $\text{VO}_2$  in response to altered oxygen demand by the tissues (Weissman et al 1984 and 1991) which may occur in response to virtually any clinical intervention and can mimic oxygen supply-dependency (Boyd et al 1992). In the present study only paralysed and sedated patients were included in order to reduce spontaneous variability in  $\text{VO}_2$  and fulfil recent recommendations for the design of oxygen kinetics studies (Pinsky 1994). In the study by Harrison et al (1991) some patients were spontaneously breathing and sedation usage was not specified. Using the chosen definition of supply-dependence only 3 of the 11 patients who received N-acetylcysteine had a significant positive relationship between  $\text{DO}_2$  and  $\text{VO}_2$ . The most significant delivery-dependence observed predicted a  $13 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  increase in  $\text{VO}_2$  when  $\text{DO}_2$  increased by  $100 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ . Changes in  $\text{VO}_2$  of greater than  $10\text{-}20 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  in response to altered  $\text{DO}_2$  have been considered indicative of clinically relevant supply-dependency (Dhainaut et al 1990). This was not observed in any of the patients despite the large range in  $\text{DO}_2$  observed during the study period in most cases. Increases in  $\text{VO}_2$  of the order observed in the present study occurring in association with increased  $\text{DO}_2$  may be a normal physiological phenomenon because of the increase in myocardial oxygen requirement which accompanies increased cardiac

work.

Harrison et al (1991) found that prostacyclin significantly increased  $\text{DO}_2$  and  $\text{VO}_2$  in patients with fulminant hepatic failure, and observed a synergistic effect between prostacyclin and N-acetylcysteine in improving  $\text{DO}_2$  and  $\text{VO}_2$ . In the present study 8 of the 11 patients who received N-acetylcysteine were also receiving prostacyclin infusion for anticoagulation during haemofiltration, but despite the concurrent use of both drugs, clinically significant supply-dependency was not observed in any individuals. A substantial increase in  $\text{DO}_2$  and  $\text{VO}_2$  during prostacyclin administration was first described in patients with sepsis and was most marked in patients who subsequently died (Bihari et al 1987). These findings have not been reproduced in subsequent studies which used either the reverse Fick method (De Backer et al 1993) or respiratory gas analysis (Hannemann et al 1994) to determine oxygen uptake. Bihari has suggested that the results of his study were confounded by inadequate fluid resuscitation and by mathematical coupling (Smithies and Bihari 1993) and it is possible that similar factors applied in Harrison and colleagues studies in fulminant hepatic failure.

Harrison et al (1991) found that N-acetylcysteine increased oxygen extraction 30 minutes after starting administration. In the present study we observed no improvement in oxygen extraction during 5 hours of infusion and observed significant decreases in OER in response to increased  $\text{DO}_2$ . It is possible that the discrepancy reflects differences between the patients studied. In the present study 6 patients who received N-acetylcysteine required noradrenaline in order to maintain a mean arterial pressure of  $\geq 60\text{mmHg}$  but the mean SVRI in the N-acetylcysteine group was still less than in those patients studied by Harrison and colleagues none of whom required vasopressor support (1123 vs 1221  $\text{dyn}\cdot\text{sec}\cdot\text{cm}^{-5}\cdot\text{m}^{-2}$ ). An inability to increase  $\text{VO}_2$  in response to increased tissue perfusion is a strong predictor of poor outcome in critically ill patients (Hayes et al 1993, Hayes et al 1997). Some of the disparity in results may have been because patients in the present study were more severely ill. It is possible that, despite randomisation, patients in the control group had less severe disease because fewer received noradrenaline or renal replacement therapy at the time the study was performed. However, at baseline there were no significant differences between the groups in haemodynamic pattern, gas



exchange data, or prothrombin time and the method of data analysis examined changes both within and between groups. Overall, the data do not support the hypothesis that N-acetylcysteine improves global measures of tissue oxygen extraction or uptake either through delivery dependent or independent mechanisms in patients with fulminant hepatic failure.

There was a variable haemodynamic response to N-acetylcysteine. In some patients cardiac output clearly increased although changes within and between the groups were not statistically different. In view of the relatively small numbers of patients in each group this could reflect type II error, although a heterogeneity of response was clearly present. Similar observations have been made in patients with liver dysfunction other than fulminant hepatic failure (Devlin et al 1997) and in patients with sepsis (Spies et al 1994, Reinhart et al 1995) in whom an inconsistent response to N-acetylcysteine occurred, although in these studies the authors only made measurements 60-90 minutes after starting the infusion. In patients with sepsis in whom cardiac output increased a lower mortality was observed in comparison with non-responders (Spies et al 1994), and it is possible that disease severity is a determinant of the haemodynamic response to the drug. If patients in the present study were sicker than those in the study by Harrison and colleagues (1991) this could explain why haemodynamic changes were less marked; significant increases in cardiac output, mean arterial pressure, and left ventricular stroke-work index (LVSWI) were all documented 30 minutes after starting the N-acetylcysteine in the earlier study. In the present study cardiovascular status was monitored for 5 hours. Previous studies in patients with sepsis syndrome (Spies et al 1994) and septic shock (Galley et al 1997) observed only transient cardiovascular changes after starting N-acetylcysteine, occurring during the first hour of infusion. These changes occurred when plasma concentrations of N-acetylcysteine are high following the loading dose. The data in the present study support the hypothesis that these changes are unpredictable and are not sustained during subsequent infusion. A recent small, randomised, controlled, double blind trial in patients with septic shock suggested that N-acetylcysteine actually depressed cardiac function over a 48 hour period (Peake et al 1996). The contrast between the immediate and delayed effects of the drug indicate the importance of evaluating its therapeutic actions over a prolonged period.

I chose not to calculate derived indices of cardiac function such as stroke volume index and LVSWI in the present study and focus on primary physiological measurements. Both stroke volume and stroke work have been widely used in the critical care literature to examine changes in cardiac function. However, these calculated variables are highly dependent on both cardiac preload and afterload and are poor indices of contractility (Parrillo 1993, Walley 1997). This is particularly the case during administration of drugs which have vasodilatory properties such as N-acetylcysteine.

There was no relationship between the total plasma N-acetylcysteine concentration and changes from baseline in any of the physiological variables examined. This was not entirely unexpected. The paucity of information regarding the metabolism and active forms of N-acetylcysteine *in vivo* was considered in the introduction to this chapter. It would have been interesting to measure reduced and oxidised forms of N-acetylcysteine, plasma cysteine concentrations, and reduced and oxidised plasma glutathione concentrations, but the facilities were unavailable. It is also likely that intracellular concentrations of these substances are of greater relevance than plasma concentrations.

A wide range of plasma concentrations was found in the patients despite using a standardised infusion regimen. In addition, the peak concentrations were lower than those typically found in patients treated within 20 hours of paracetamol overdose (Prescott et al 1989). The study was not designed for pharmacokinetic analysis and insufficient samples were collected to enable this. Reduced peak plasma concentrations may have occurred because of enhanced metabolism or an increase in the volume of distribution of the drug in fulminant hepatic failure. The drug is primarily distributed into extracellular water (Borgstrom et al 1986, Olson et al 1988) and it is likely that in patients with fulminant hepatic failure, in whom oedema secondary to capillary leak is a frequent feature, the volume of distribution of the drug is increased. The data in this study indicate the need for pharmacokinetic and pharmacodynamic studies of N-acetylcysteine in critically ill patients in order to utilise this drug appropriately.

This study indicates that global improvements in tissue oxygen delivery and uptake are an unlikely mechanism of action of N-acetylcysteine in patients with severe fulminant hepatic failure. This conclusion contrasts with that of Harrison and colleagues (1991) and I have

argued that there were many confounding factors in that study. My conclusion is in keeping with recent work which suggests that pathological oxygen supply dependency does not exist in most resuscitated critically ill patients (Russell and Phang 1994, Gasman et al 1996) and that optimising haemodynamic variables to supranormal physiological levels does not confer any survival benefit (Hinds and Watson 1995, Heyland et al 1996).

## **Conclusions**

- 1) Clinically significant pathological supply dependency is not present during N-acetylcysteine infusion in patients with fulminant hepatic failure. Methodological factors explain many of the contradictory results of earlier studies.
- 2) N-acetylcysteine infusion does not improve global indices of tissue oxygenation in patients with fulminant hepatic failure.
- 3) The place of N-acetylcysteine in the treatment of critically ill patients is unclear, and the mechanism of action of the drug incompletely understood.

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### ENERGY EXPENDITURE IN FULMINANT HEPATIC FAILURE

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#### OBJECTIVES

The objectives of this chapter were:

- 1) To measure energy expenditure in a homogeneous group of patients with paracetamol-induced fulminant hepatic failure.
- 2) To compare this group of patients with healthy control subjects and with physically anhepatic patients studied during liver transplantation.
- 3) To investigate the clinical determinants of energy expenditure in patients with paracetamol-induced fulminant hepatic failure.
- 4) To investigate the value of predictive formulae for estimating energy requirements in patients with fulminant hepatic failure.
- 5) To investigate the nature of the acute phase response in patients with paracetamol-induced fulminant hepatic failure and its relationship to energy expenditure.

#### BACKGROUND

There is a large literature concerning the effect of many types of critical illness on energy expenditure (Chiolero et al 1997, Burzstein et al 1989). These indicate that increases of the order of 30-50% over resting energy expenditure are associated with multiple trauma and sepsis. There is, however, only one previous study which examines energy expenditure in patients with acute liver failure (Schneeweiss et al 1993). The factors which influence energy expenditure in acute hepatic failure are extremely complex in comparison with other forms of critical illness. The liver normally accounts for approximately 25% of basal metabolic rate (Ganong 1991). These figures are consistent with the decreases in whole body oxygen consumption typically observed following hepatectomy in patients with chronic liver disease undergoing liver transplantation (Svensson et al 1989). The metabolic function of the

liver is severely deranged in fulminant hepatic failure as evidenced by the profound decreases in synthetic and detoxification functions which accompany the condition. It has been estimated that at least 85% of functioning liver cell mass is destroyed in fulminant hepatic failure (Ramsøe et al 1980). It might therefore be anticipated that a decrease in energy expenditure accompanies this condition. Patients with fulminant hepatic failure frequently demonstrate clinical features of a stress response such as fever and tachycardia. Severe fulminant hepatic failure is frequently accompanied by a high cardiac output, low systemic vascular resistance and hypotension, similar to patients with septic shock in whom energy expenditure is increased (Voerman et al 1993). Complications such as acute renal failure, infection, cerebral oedema, and tissue hypoperfusion may each have an effect. Finally, treatments such as mechanical ventilation, sedation, and vasopressor drugs all influence metabolic rate (Chiolero et al 1997).

In their study in patients with acute liver failure, Schneeweiss and colleagues (1993) examined 12 patients with acute liver failure of variable severity. The degree of encephalopathy varied between I and IV and prothrombin time from 31 to >160 seconds. Only one patient required haemodynamic support with vasopressor drugs and cardiac output was not measured in any cases. Only one patient was undergoing mechanical ventilation and it is unclear if any patients received sedative drugs. The aetiology of liver failure was hepatitis B (5), *Amanita phalloides* poisoning (3), non-A non-B hepatitis (3), and halothane hepatitis (1). The principal findings of the study were that energy expenditure was increased by approximately 30% in patients with acute hepatic failure in comparison with matched healthy control subjects.

Several questions are raised by this well-conducted study. Firstly, do patients with paracetamol-induced fulminant hepatic failure have a similar level of energy expenditure. The mechanism of hepatic injury is different in these patients (Flanagan and Meredith 1991) and the onset of disease is frequently more rapid than in viral hepatitis. The different criteria associated with poor outcome for paracetamol and non-paracetamol induced fulminant hepatic failure reflect these differences (O'Grady



et al 1989). Secondly, patients with Grade III or IV encephalopathy resulting from paracetamol-induced fulminant hepatic failure are usually tracheally intubated and mechanically ventilated for airway protection, and to facilitate monitoring and treatment. Energy expenditure under these circumstances may be altered by the administration of drugs or vasopressor agents. The determination of energy expenditure is clinically relevant to the administration of nutrition in these patients, particularly as hepatic handling of substrate is likely to be significantly impaired.

## **MATERIALS AND METHODS**

### **Patients**

16 patients with paracetamol-induced fulminant hepatic failure were studied. All patients were in grade III/IV hepatic encephalopathy and receiving mechanical ventilation via an endotracheal tube using a Servo 900C ventilator. All patients were sedated with propofol ( $1\text{-}2\text{mg.kg}^{-1}.\text{hour}^{-1}$ ) and alfentanil ( $10\text{-}40\mu\text{g.kg}^{-1}.\text{hour}^{-1}$ ) by infusion and were paralysed with atracurium ( $0.5\text{-}1.5\text{mg.kg}^{-1}.\text{hour}^{-1}$ ). Blood pressure was monitored continuously using an indwelling arterial catheter and cardiac output was measured semi-continuously using a pulmonary artery catheter and cardiac output computer (Baxter Vigilance system). Patients were studied within 24 hours of instituting mechanical ventilation following resuscitation with fluids and vasoconstrictors as clinically indicated. Studies were only performed during periods of cardiovascular stability when changes in haemodynamic support were not required. Patients who required renal support were receiving continuous venovenous haemofiltration throughout the study period.

### **Energy Expenditure Measurements**

Metabolic measurements were made with the Deltatrac metabolic monitor. Prior to each measurement the machine was calibrated against a standard gas mixture (95% oxygen, 5% carbon dioxide) and ambient barometric pressure. Calibration was also checked 3 monthly using an alcohol burning test.



*Ventilated patients:* Measurements were made in the respirator mode using inspiratory gas sampling and collection of all expired gas from the ventilator. A careful check for leaks in the system or around the endotracheal tube was made prior to commencing measurement and no changes to FIO<sub>2</sub> or ventilator settings were made during, or for one hour preceding, the measurement period.

*Spontaneously breathing subjects:* Volunteers were studied following an overnight fast in a quiet thermoneutral room with subjects supine and breathing air. Measurements were made in the canopy mode for a total of 40 minutes (10 minutes acclimatisation, 30 minutes steady state measurement).

After measurements had reached a steady state oxygen consumption, carbon dioxide elimination, and respiratory quotient (RQ) were measured each minute for 30 minutes and the mean energy expenditure calculated for the period. Interventions known to alter oxygen consumption in ventilated patients such as physiotherapy, tracheal suction, and turning (Weissman et al 1984) were not carried out during or for one hour prior to metabolic measurements. Previous studies have shown that a 30 minute period of measurement approximates closely to total energy expenditure in critically ill patients, particularly under conditions of coma and deep sedation (Weissman et al 1986, Frankenfield et al 1994).

At the start of each 30 minute study period hemodynamic variables and pulmonary artery temperature were recorded, and arterial blood was sampled and analysed for whole blood lactate concentration and acid-base status using a YSI 2300 Stat Plus analyser and an IL BGE 1400 series respectively. All measurements were carried out within 5 minutes of sample collection. No patient received parenteral or enteral nutrition during the 12 hours prior to or during the study. If required intravenous glucose was administered to keep blood glucose concentration between 4-6mmol.l<sup>-1</sup>.

Energy expenditure for each subject was expressed in kJ.kg<sup>-1</sup>.hour<sup>-1</sup>. In addition to raw data a temperature-corrected estimation of energy expenditure was calculated for

each patient in the fulminant hepatic failure and anhepatic liver transplant groups using a correction factor of 10% per °C in accordance with the study by Manthous et al (1995). Predicted resting energy expenditure was also calculated for each of the patients with fulminant hepatic failure using the Harris-Benedict equation, and corrected to 37°C using the same algorithm.

### *Control Groups*

*Liver Transplantation:* 16 patients undergoing uncomplicated elective liver transplantation were studied. In all cases the piggyback surgical technique was used. Inferior vena caval blood flow was maintained throughout the anhepatic period by use of a side-clamping vena caval clamp and portal venous drainage was maintained in all cases via a temporary portacaval shunt. During the period of measurement all patients were anaesthetised using propofol ( $6\text{mg.kg}^{-1}.\text{hour}^{-1}$ ), alfentanil ( $30\text{-}40\mu\text{g.kg}^{-1}.\text{hour}^{-1}$ ), and midazolam ( $0.2\text{mg.kg}^{-1}.\text{hour}^{-1}$ ) by infusion and muscle paralysis was maintained with atracurium ( $0.5\text{-}1.5\text{mg.kg}^{-1}.\text{hour}^{-1}$ ). All patients received dopamine  $2\text{-}3\mu\text{g.kg}^{-1}.\text{min}^{-1}$  throughout the procedure. The mean energy expenditure for a 30 minute period from 10 to 40 minutes after the start of the anhepatic period (defined as the time of application of the inferior vena caval clamp at the level of the hepatic veins) was calculated. Raw data were corrected to 37°C using the same algorithm described above.

*Healthy volunteers:* 16 healthy volunteers were studied. Subjects were chosen to represent an age and sex matched control group with reference to the fulminant hepatic failure patients.

### **Measurements of Cytokines and C-reactive protein (CRP) concentrations.**

CRP, IL-6, and TNF concentrations were measured in 10 of the patients with paracetamol-induced fulminant hepatic failure, and in a group of 6 healthy subjects matched for age and sex. Control subjects in this part of the study were selected at the time batch analyses were performed and were different from those in whom energy expenditure was measured.

Blood was drawn from the arterial catheter and immediately centrifuged. Serum was divided into aliquots and stored at -60°C for subsequent analysis.

### *Cytokine Assays*

#### *Measurement of IL-6 and TNF.*

Measurement of IL-6 and TNF in plasma was performed by enzyme-linked immunosorbent assay (ELISA)(Goldie et al 1995). For IL-6, microtitre plates (Costar, High Wycombe, UK) were coated with monoclonal anti-IL-6 antibody (Boehringer-Mannheim) at  $2\mu\text{g.ml}^{-1}$  in 50mM  $\text{NaCO}_3/\text{NaHCO}_3$  pH 9.6 for 4 hours at room temperature. Samples were diluted 1/5 in 20mM Tris-buffered saline pH 7.4 containing 1% bovine serum albumin (TBS-BSA) and incubated at 4°C for 18 hours. The second antibody was goat polyclonal anti-IL-6 (R&D Systems, Abingdon, UK) at  $2\mu\text{g.ml}^{-1}$ . These were detected with peroxidase-conjugated anti-goat IgG Fab fragments (Boehringer-Mannheim, Lewes, UK). For TNF, paired antibodies (Boehringer-Mannheim, Lewes, UK) were used in accordance with manufacturers instructions. Standard curves for each ELISA were constructed using recombinant human IL-6 or TNF (R&D systems, Abingdon, UK). The substrate was 3,3', 5,5'-tetramethylbenzidine (TMB) in 100mM sodium acetate/citrate, pH 4.9. The reaction was stopped with 100 $\mu\text{l}$  of 1M sulphuric acid per well and plates were read at 490nm using a Dynatech MR5000 plate reader. Cytokine concentrations in samples were calculated from standard curves calculated using Assaytop computer software (Biosoft, Cambridge, UK). The reproducibility for these assays determined within the laboratory was good (table 4.1)

TABLE 4.1: Coefficients of variation (%CV) for the measurement of IL-6 and TNF and sensitivity by ELISA using the method described.

	Intra assay %CV	Inter assay %CV	Sensitivity pg.ml <sup>-1</sup>
IL-6	3	6	75
TNF	5	8	15

*Measurement of C-reactive protein in sera*

CRP concentrations in plasma were measured by sandwich ELISA. 96 well plates were coated with goat anti-human CRP at a dilution of 1:5000. Plates were blocked using 1 % BSA prior to washing. Sera were diluted 1:10 000 and were added to the coated plates. Standard curves were constructed using human C-reactive protein calibrator (Dako, Glostrup, Denmark). Samples and standards were incubated overnight and following washing, the second antibody, peroxidase conjugated anti-human CRP, was added. The substrate used was TMB and the reaction was stopped using 1M sulphuric acid. Plates were read at 490nm using a Dynatech MR5000 automated plate reader. Concentrations in samples were calculated from standard curves using Assaytop computer software. The lower limit of sensitivity taking into account sample dilutions was 100µg.ml<sup>-1</sup> (table 4.2).

TABLE 4.2: Coefficients of variation (%CV) and sensitivities of ELISA for measurement of serum CRP concentration.

	Intra assay %CV	Inter assay %CV	Sensitivity (mg.l <sup>-1</sup> )
CRP	7	15	1

*Statistical analysis:* The agreement and bias between energy expenditure measurements and predicted energy expenditure by the Harris-Benedict formula were compared with the Bland and Altman method. Differences between the fulminant hepatic failure group and each control group were examined using Student's t test. Differences within the fulminant hepatic failure group were examined using the Mann-Whitney U test. Relationships between physiological variables and energy expenditure within the fulminant hepatic failure group were investigated by calculating the product moment correlation coefficient.

For the cytokine data comparisons between the fulminant hepatic failure group and control group were made using the Mann-Whitney U test. Correlations between variables were made by calculating Spearman's Rank Correlation Coefficient.

$P < 0.05$  was considered statistically significant.

## RESULTS

The clinical characteristics of the patients with fulminant hepatic failure are shown in Table 4.3. Cardiac index was elevated in all cases and 5 patients were receiving noradrenaline at the time of study. Patients were hyperlactataemic, but the acid-base disturbance which accompanied this abnormality varied widely between patients. Data for patients studied during the anhepatic period of liver transplantation, and for healthy volunteers, are shown in table 4.5.

Energy expenditure data for the patients with fulminant hepatic failure is shown in Tables 4.4 and compared with the control groups in table 4.5 and figure 4.1. There was no relationship between energy expenditure and cardiac index ( $r = -0.17$ ), or heart rate ( $r = -0.28$ ). No difference in energy expenditure was found between patients with or without acute renal failure, or between patients receiving noradrenaline and those with an adequate blood pressure without the need for vasoconstrictor support.

The pulmonary artery blood temperature varied between patients as a result of muscle paralysis, fluid administration, and haemofiltration, but there was no overall relationship between blood temperature and energy expenditure within the fulminant hepatic failure group ( $r = 0.35$ ). There was a weak correlation between glucose requirement and the RQ ( $r = 0.57$ ,  $p < 0.05$ ).

The agreement between predicted and measured energy expenditure for the fulminant hepatic failure patients was poor even after correction for temperature (table 4.6). There was no overall bias between the methods (mean bias  $-0.13$  (95% confidence intervals  $-0.54$  to  $0.28$ )  $\text{kJ.kg}^{-1}.\text{hour}^{-1}$ , but the limits of agreement were wide and clinically highly significant (limits of agreement  $-1.63$  to  $1.37$   $\text{kJ.kg}^{-1}.\text{hour}^{-1}$ , figure 4.2).

Uncorrected energy expenditure in patients with fulminant hepatic failure was 18% higher than in healthy control subjects ( $p = 0.0005$ ) and was 24% higher after correction for temperature differences ( $p = 0.0001$ ). The healthy control group was well-matched for age, sex, and weight (Table 4.5). In comparison with the patients studied during the anhepatic phase of liver transplantation temperature-corrected energy expenditure was 29% greater in the fulminant hepatic failure group ( $p < 0.0001$ , Table 4.5). The group data are illustrated in figure 4.1. Patients undergoing liver transplantation were significantly older because of the differing aetiology of liver disease.



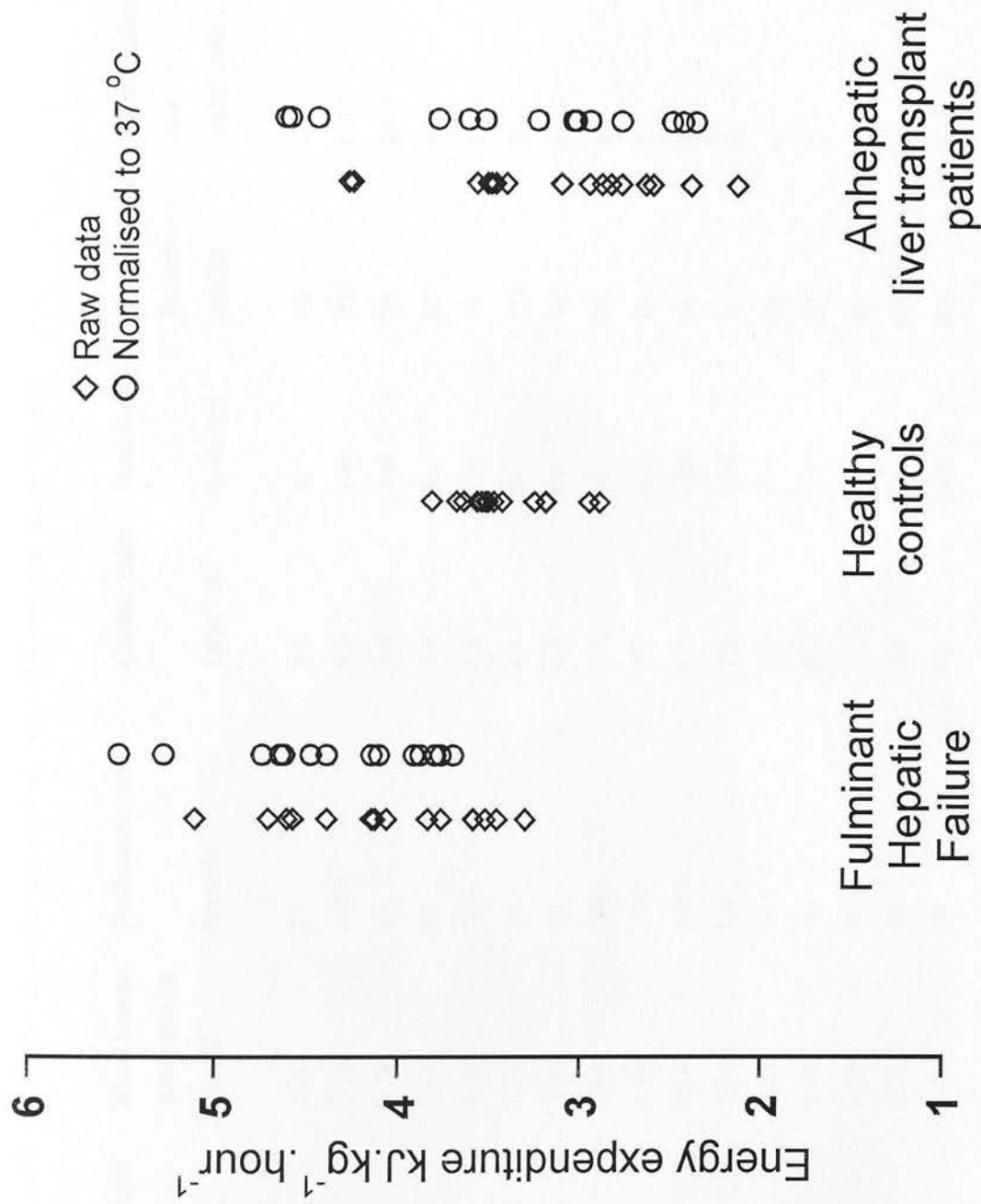


Figure 4.1: Energy expenditure in patients with FHF compared with healthy controls ( $P=0.0001$ ) and anhepatic liver transplant patients ( $P=0.0001$ )

TABLE 4.3: Characteristics of the patients with paracetamol-induced fulminant hepatic failure.

Patient	Age	Base Excess mmol.l <sup>-1</sup>	Blood Lactate concentration mmol.l <sup>-1</sup>	Prothrombin time Seconds	Cardiac index l.min <sup>-1</sup> .m <sup>-2</sup>	Heart Rate beats.min <sup>-1</sup>	Mean Arterial Pressure mmHg	Noradrenaline dose µg.kg <sup>-1</sup> .min <sup>-1</sup>	Acute renal failure Y: yes; N: no	Outcome
1	25	-3.6	1.01	57	4.4	86	80	0	Y	S
2	25	-8.3	2.96	>180	6.5	140	75	0.07	Y	T
3	59	1.6	4.28	89	5.0	105	70	0.07	Y	D
4	16	4.8	2.98	84	7.4	86	93	0.07	Y	S
5	18	-8.1	6.20	105	4.3	115	91	0.35	Y	T
6	22	-3.4	2.38	74	4.4	93	116	0	Y	T
7	42	7.7	3.06	60	4.0	99	91	0	Y	S
8	17	0.7	1.88	100	3.9	98	76	0	Y	S
9	39	3.5	3.78	>180	6.0	111	72	0	Y	D
10	21	-8.5	15.40	>180	5.7	150	54	1.6	Y	D
11	21	-9.8	5.7	110	7.2	136	79	0	Y	D
12	20	9.7	1.57	66	3.1	87	89	0	N	S
13	23	7.1	1.45	78	5.6	112	77	0	N	S
14	21	0.4	2.00	81	5.1	80	98	0	N	D
15	25	7.5	2.09	101	5.3	80	92	0	N	S
16	54	0.7	1.06	78	4.0	104	81	0	N	S

S, survived; D, died; T, underwent liver transplant

TABLE 4.4: Energy expenditure measured by indirect calorimetry in patients with paracetamol-induced fulminant hepatic failure. All values mean (SD).

Patient	VO <sub>2</sub> ml.min <sup>-1</sup>	VCO <sub>2</sub> ml.min <sup>-1</sup>	RQ	MREE kJ.kg <sup>-1</sup> .hour <sup>-1</sup>	Temperature °C	TC REE kJ.kg <sup>-1</sup> .hour <sup>-1</sup>
1	206(13)	169(5)	0.82(0.04)	4.07	36.8	4.15
2	193(8)	152(4)	0.79(0.02)	4.13	35.8	4.63
3	298(10)	249(4)	0.84(0.03)	3.77	36.6	3.92
4	231(7)	226(3)	0.98(0.03)	5.11	36.2	5.51
5	230(6)	212(5)	0.92(0.02)	4.61	36.7	4.75
6	178(4)	136(3)	0.76(0.01)	3.46	36.3	3.70
7	299(7)	227(6)	0.75(0.00)	4.39	36.8	4.48
8	243(12)	178(4)	0.73(0.02)	4.71	35.8	5.28
9	168(14)	135(3)	0.80(0.05)	3.30	35.5	3.80
10	176(4)	166(2)	0.93(0.02)	3.59	36.5	3.77
11	190(6)	166(5)	0.87(0.01)	4.15	35.8	4.65
12	233(11)	182(8)	0.78(0.02)	4.58	37.4	4.39
13	299(6)	209(3)	0.70(0.01)	4.07	36.9	4.11
14	165(4)	130(3)	0.78(0.01)	3.52	36.2	3.80
15	262(9)	196(4)	0.75(0.02)	3.84	36.9	3.88
16	194(9)	168(5)	0.87(0.02)	3.59	36.7	3.70
Mean	223(47)	181(36)	0.81(0.07)	4.05(0.52)	3.91(0.58)	4.28(0.56)

VO<sub>2</sub> oxygen consumption; VCO<sub>2</sub> carbon dioxide production; RQ respiratory quotient; MREE measured resting energy expenditure; PREE predicted resting energy expenditure (Harris-Benedict equation); TC REE measured resting energy expenditure corrected to 37°C using 10%°C<sup>-1</sup>.

TABLE 4.5: Resting energy expenditure in patients with fulminant hepatic failure, age/sex matched healthy control subjects, and patients with chronic liver disease studied during the anhepatic period of liver transplantation. Mean (SD).

	Fulminant Hepatic Failure	Healthy Controls	Anhepatic Patients
Number	16	16	16
Age	29 (14)	33 (8)	53 (7)
Weight (kg)	65 (12)	69 (11)	65 (15)
Sex (F/M)	11/5	11/5	13/3
MREE (kJ.kg <sup>-1</sup> /hour <sup>-1</sup> )	4.05 (0.52)	3.44 (0.27) * †	3.15 (0.61) ††
TC REE (kJ.kg <sup>-1</sup> /hour <sup>-1</sup> )	4.28 (0.56)	-	3.32 (0.73) †††

MREE measured resting energy expenditure; TC REE measured resting energy expenditure corrected to 37°C using 10%°C<sup>-1</sup>

\* p=0.0005 compared with MREE in liver failure group, † p=0.0001 compared with TC REE in liver failure group, †† p=0.0001 compared with MREE in liver failure group, ††† p<0.0001 compared with TC REE in liver failure group.

Figure 4.2: Bland and Altman plot comparing measured with predicted energy expenditure (from the Harris-Benedict equation) in patients with fulminant hepatic failure. All values corrected to normothermia.

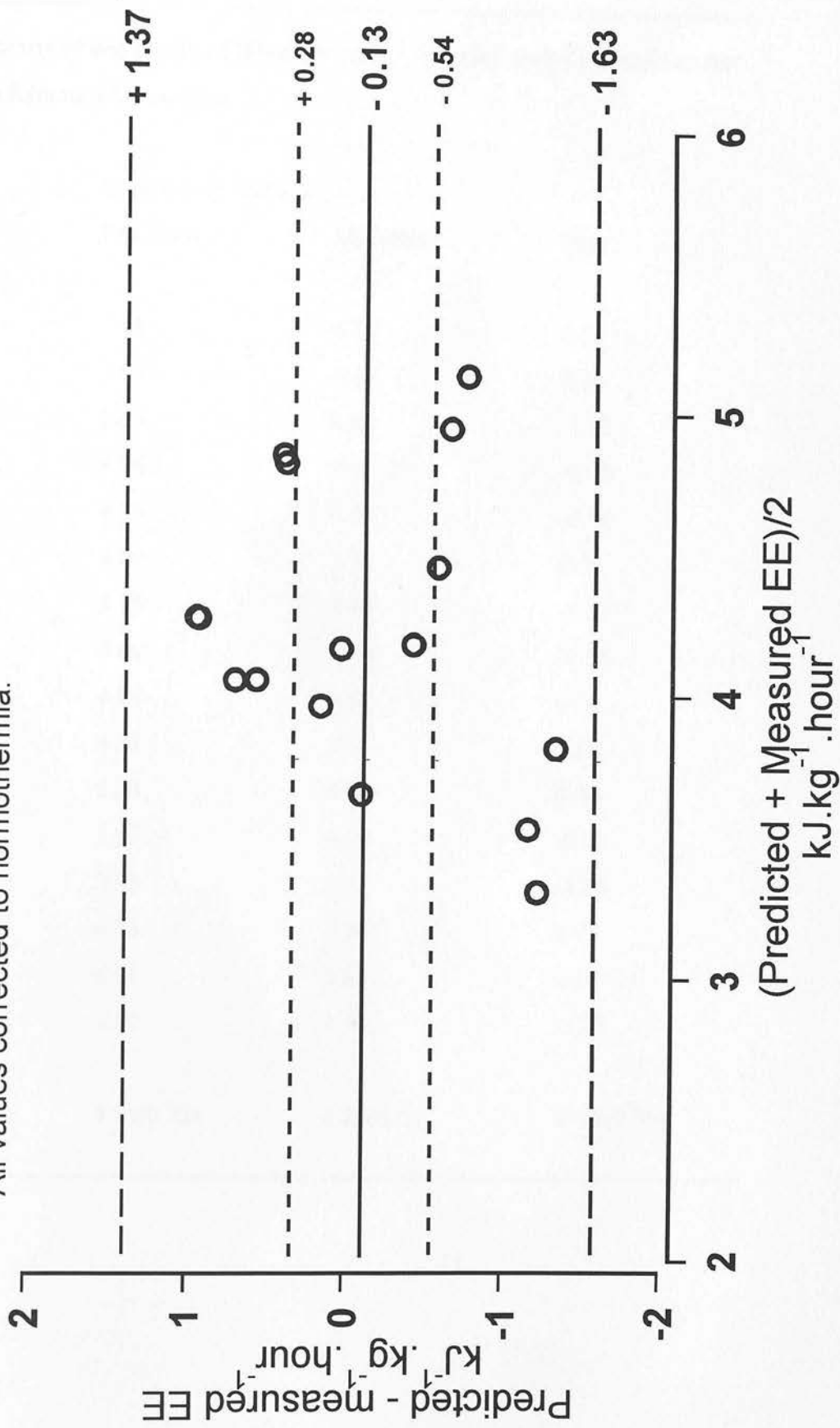


Table 4.6: Measured and predicted (Harris-Benedict formula) energy expenditure for patients with fulminant hepatic failure.

Patient	Energy Expenditure		
	Predicted	Measured	Bias
1	4.18	4.15	0.03
2	5.01	4.63	0.38
3	2.69	3.92	-1.22
4	4.75	5.51	-0.76
5	4.16	4.75	-0.58
6	4.40	3.70	0.70
7	3.15	4.48	-1.33
8	4.61	5.28	-0.66
9	4.74	3.80	0.94
10	4.33	3.77	0.56
11	5.04	4.65	0.40
12	3.97	4.39	-0.43
13	2.95	4.11	-1.16
14	4.73	3.80	0.93
15	4.04	3.88	0.16
16	3.60	3.70	-0.10
Mean (SD)	4.15(0.72)	4.28(0.56)	-0.13(0.76)



Data for plasma cytokine and CRP concentrations are illustrated in figure 4.3. The median plasma CRP concentration was 71(range 8-100)mg.l<sup>-1</sup>; CRP was not detected in the healthy volunteers (P<0.01). The patients with fulminant hepatic failure had significantly elevated concentrations of TNF (130[0-350]pg.ml<sup>-1</sup>) and IL-6 (1.0[0-11.4]ng.ml<sup>-1</sup> in comparison with healthy volunteers (TNF and IL-6 not detected, P<0.01 in both cases)(figure 4.3). No correlation was found between CRP and IL-6 or TNF, or between IL-6 and TNF concentrations. There was no significant relationship between energy expenditure and IL-6, TNF, or CRP concentrations.

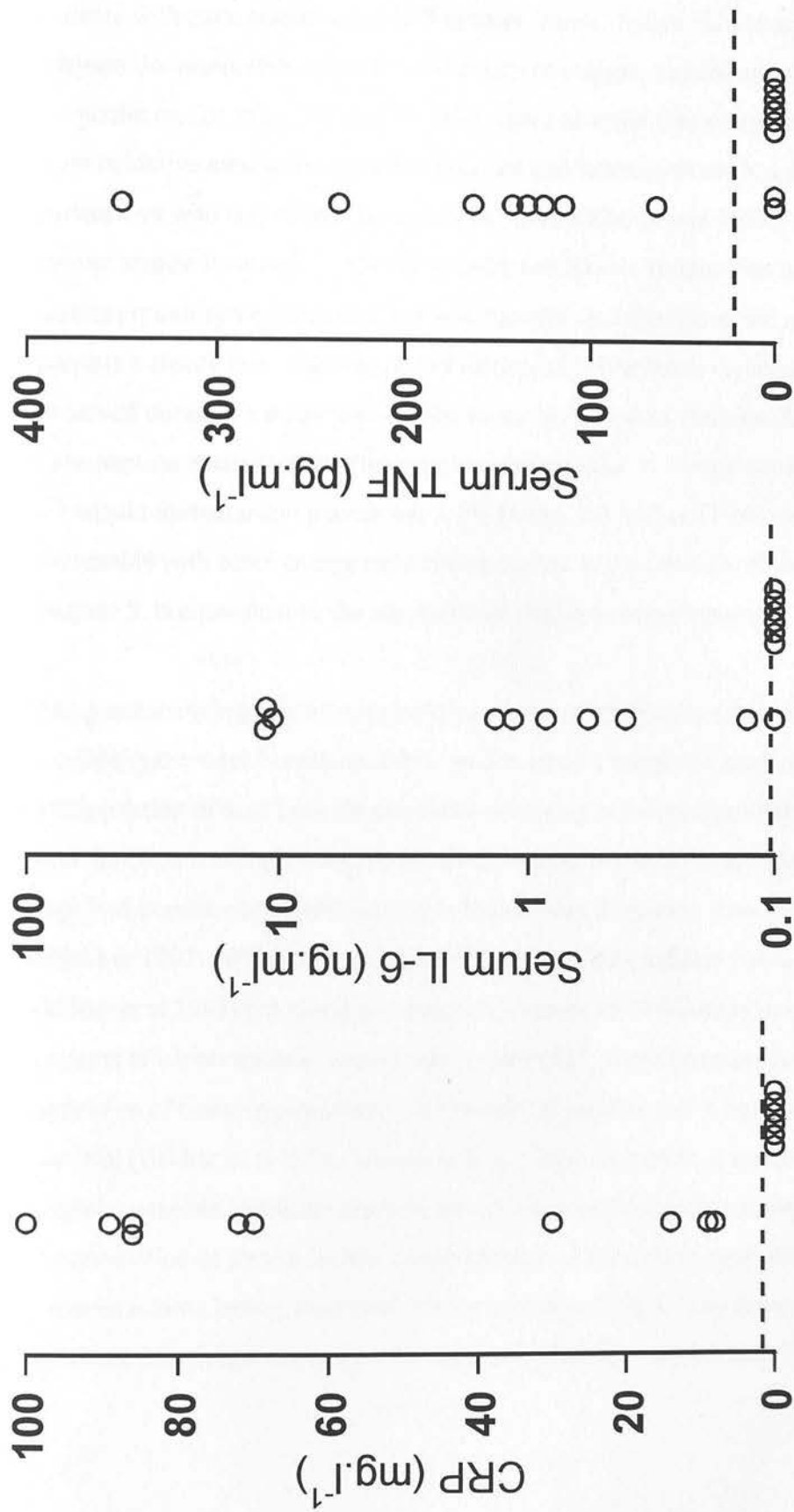


Figure 4.3: Serum concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor (TNF) in patients with paracetamol-induced fulminant hepatic failure (n=10, left side) and in healthy controls (n=6, right side). Limits of detection for the assays are shown with dashed lines.  $P < 0.01$  between fulminant hepatic failure patients and control subjects for CRP, IL-6, and TNF.

## DISCUSSION

The data indicate that energy expenditure is 20-25% higher in ventilated critically ill patients with paracetamol-induced fulminant hepatic failure than in awake healthy control subjects. In interpreting the data several factors require consideration. The estimation of metabolic rate by means of indirect calorimetry assumes that energy is derived entirely from oxidative metabolism of substrates and that individuals are in a steady state, particularly with regard to carbon dioxide balance (Ferraninni 1988). Factors known to disrupt steady state such as altered alveolar ventilation, sudden changes in cardiorespiratory variables or rapid acid-base balance disruption did not occur. In all patients a steady state was attained as evidenced by the small variation in measurement observed during the study period. The mean coefficient of variation for oxygen consumption measurements (the principal determinant of energy expenditure) during the 30 minute measurement period was 3.7% (range 2.0-8.3%) which compares extremely favourably with other energy expenditure studies in the critically ill and, as documented in chapter 2, is equivalent to the resolution of Deltatrac measurements.

The presence of significant anaerobic metabolism in some patients was difficult to exclude; most were hyperlactataemic, and in some a metabolic acidosis was present. The interpretation of acid-base abnormalities occurring in association with severely impaired liver function is complex. Metabolic alkalosis may occur because of hypokalaemia or impaired hepatic urea synthesis, and is found more frequently than metabolic acidosis (Hawker 1993). When present, metabolic acidosis may indicate tissue hypoperfusion (Bihari et al 1985) but could also result from acute renal failure which was present in all 6 patients in whom the base excess was  $< -2\text{mmol.l}^{-1}$ . Hyperlactataemia is often considered indicative of tissue hypoperfusion in critically ill patients and is associated with reduced survival (Bakker et al 1991, Marecaux et al 1996). However, it is recognised that hyperlactataemia and lactic acidosis are not equivalent (Hotchkiss and Karl 1992). Accumulation of plasma lactate, in the absence of anaerobic metabolism, can result from reduced plasma lactate clearance, accelerated glycolysis, or impairment of the enzyme pyruvate dehydrogenase (a primary regulator of aerobic glycolysis). These processes

occur in patients with sepsis (Hotchkiss and Karl 1992), and may be present during fulminant hepatic failure. In particular, plasma lactate clearance is reduced in the presence of hepatic and renal insufficiency (Kriesberg 1980). My own study with N-acetylcysteine, and a study by Hanique and colleagues (1994a), indicate that increasing oxygen delivery in patients with fulminant hepatic failure does not increase global oxygen consumption or decrease plasma lactate concentrations. Thus although it was not possible to exclude the presence of anaerobic metabolism in some of the patients with fulminant hepatic failure, the presence of metabolic acidosis and hyperlactataemia cannot be considered reliable indicators in this group of patients. Furthermore, indirect calorimetry underestimates rather than exaggerates total energy expenditure in the presence of significant anaerobic metabolism, which would not alter the principal findings of the study.

Urinary nitrogen excretion was not measured and as a result oxidation rates for individual substrates could not be calculated in the patients. The accurate assessment of nitrogen balance in patients with renal failure requiring haemofiltration, and in patients in whom an abnormal distribution of body fluids is present, is extremely difficult, and these were both features in most of the patients with fulminant hepatic failure. Calculation of energy expenditure from  $\text{VO}_2$  and  $\text{VCO}_2$  alone, without accurate nitrogen excretion data, has a negligible effect on energy expenditure estimations even in hypermetabolic critically ill patients (Burzstein et al 1977, Burzstein et al 1989). Thus a 100% error in the measurement of urinary nitrogen excretion causes an error of only 1% in the calculation of energy expenditure (Burzstein et al 1989).

As a result of muscle paralysis, and heat loss from haemofiltration circuits or during surgery, many of the patients with fulminant hepatic failure and those studied during transplantation were hypothermic. Under these circumstances the normal counter-regulatory mechanisms which generate heat through muscle activity are abolished. Manthous and colleagues (1995a) found a close relationship between  $\text{VO}_2$  and body temperature during cooling of critically ill febrile patients equivalent to approximately 10% change per  $^{\circ}\text{C}$ . In view of the significant influence of body temperature on metabolic

rate, and the wide range of temperature values in the patients studied, I normalised data to 37°C assuming changes of 10%.°C<sup>-1</sup>. However, the differences in energy expenditure between the groups studied were of similar magnitude and significance both before and after applying this correction factor.

Energy expenditure was 20-25% higher in patients with fulminant hepatic failure compared to matched awake healthy subjects. The patients with acute liver failure were all fully paralysed with muscle relaxant drugs and sedated with hypnotic and opioid drugs. These agents have all been shown to significantly decrease energy expenditure in comparison to the awake spontaneously breathing state. Mechanical ventilation in conjunction with muscle paralysis reduces oxygen consumption in critically ill patients by 20-25% (Manthous et al 1995b, Viale et al 1988, Marik and Kaufman 1996, Boulanger et al 1994), and opioid analgesia and sedative drugs have each been shown to decrease energy expenditure by more than 10% (Swinamer et al 1988, Boyd et al 1992). Taking these additional factors into account the data indicate that metabolic rate is substantially increased in patients with paracetamol-induced fulminant hepatic failure in comparison with healthy control subjects. This conclusion is consistent with the study by Schneeweiss and colleagues (1993) who found metabolic rate was approximately 30% higher in a heterogeneous group of patients with non paracetamol-induced acute hepatic failure than in control subjects. In that study patients were not sedated or paralysed and only 1 of the 12 patients studied was mechanically ventilated.

In the patients with fulminant hepatic failure the agreement between predicted and measured energy expenditure was poor even after correction for temperature. Previous studies have shown that the predictive value of the Harris-Benedict and other equations used for estimating energy expenditure is low in critically ill patients, and that these equations frequently give misleading results (Chiolero et al 1997). Various stress factors have been suggested for use with predictive equations in order to correct for the effects of altered temperature, and other factors such as injury severity. The patient group in the present study was relatively homogeneous in terms of diagnosis, illness severity, and

method of treatment. The low predictive value of the Harris-Benedict equation even after normalising data to 37°C indicates that direct measurement of energy expenditure in individual patients is advisable when an accurate assessment of metabolic rate is required.

There were no significant correlations between energy expenditure and haemodynamic variables, temperature, or noradrenaline requirements and there was no difference between patients with or without renal failure, although numbers for comparison were small. The absence of an association between these factors, which are frequently linked with energy expenditure, was surprising, but presumably reflects the complex nature of the metabolic response in patients suffering from fulminant hepatic failure, and the influence of drug therapy on cardiovascular variables.

Patients were studied in the fasting state in order to eliminate the effects of substrate-induced thermogenesis. Patients who were hypoglycaemic on bedside testing received dextrose by infusion and this was titrated to ensure normoglycaemia. The thermogenic effect of carbohydrate is small and is unlikely to have influenced the results significantly. Schneeweiss et al (1993) found that glucose supply in patients with acute liver failure was able to normalise substrate utilisation, presumably by counteracting the effects of impaired liver glucose metabolism. There was a weak correlation between the respiratory quotient and the rate of glucose infusion which suggests that, in the absence of normal hepatic glucose release, exogenous glucose supply was a major source of substrate for oxidation.

Measured energy expenditure was approximately 29% higher in patients with fulminant hepatic failure than in patients undergoing elective liver transplantation who were physically anhepatic. These patients were also paralysed and sedated and in this respect were directly comparable with the fulminant hepatic failure group. Energy expenditure in the patients undergoing transplantation may have been affected by their underlying disease or by the stress response to surgery, and these patients were also older than the fulminant hepatic failure group. The administration of "renal dose" dopamine in these



patients may also have had a thermogenic effect. Despite these confounding factors the data provide further evidence that, despite the loss of functioning liver cell mass, metabolic rate in patients with fulminant hepatic failure is not equivalent to an anhepatic state. It is clear from the present study that other factors substantially increase metabolic rate in this disease.

Infection is a common complication of fulminant hepatic failure and the presence of infection during critical illness is associated with increased energy expenditure (Kreymann et al 1993, Chioloro et al 1997). The patients in the present study were all studied within 24 hours of admission to the intensive care unit when septic complications are relatively rare in fulminant hepatic failure. Routine microbiological screening also failed to detect evidence of infection in any patients and I consider it unlikely that this was a contributing factor.

Plasma concentrations of CRP, TNF, and IL-6 were all significantly elevated in the patients. TNF is activated early in the course of the inflammatory response and infusion of TNF reproduces the clinical features of the systemic inflammatory response in humans (Blackwell and Christman 1996). Animal studies of paracetamol-induced hepatotoxicity have shown that TNF appears in the plasma within hours of paracetamol administration and subsequently decreases in a phasic manner (Blazka et al 1995). Similar findings have been made in models of sepsis, and some human studies suggest that the magnitude and duration of the TNF response is associated with survival (Blackwell and Christman 1996). No correlations between survival or other clinical variables were demonstrated in the present study but numbers were small and measurements were only made on one occasion. Similar findings were made by Sekiyama and colleagues (1994) in patients with virus-induced liver failure. TNF is also renally cleared and the presence of acute renal failure in many of the patients means that interpretation of plasma concentrations is not straightforward. IL-6 is produced by many cell types and plasma concentrations usually increase after the peak in TNF and possibly in response to it. The exact function of IL-6 in the inflammatory response is incompletely understood. In experimental animals infusion

of IL-6 does not reproduce a sepsis-like state and blocking with monoclonal antibodies does not appear to be beneficial (Blackwell and Christman 1996). However, IL-6 concentrations appear to correlate more closely with outcome than any other cytokine. Several groups have documented an association between high plasma IL-6 concentrations and subsequent death in septic patients (Blackwell and Christman 1996, Goldie et al 1995), and Izumi and colleagues (1994) made a similar observation in patients with fulminant hepatic failure.

Plasma CRP concentrations were elevated in all patients. The plasma half-life of CRP in humans is 19 hours and it is not known to be stored significantly in hepatocytes. It is therefore likely that, despite the presence of severe liver damage, hepatocytes were continuing to generate an acute phase protein response. This finding is consistent with studies by Sekiyama et al (1994) in viral liver failure, and Izumi et al (1994) in a mixed group of patients with fulminant hepatic failure. The levels of CRP found in these and the present study are significantly lower than is usually associated with sepsis, which may reflect the reduced synthetic ability of the liver in fulminant hepatic failure. IL-6 is a potent stimulus for CRP production by hepatocytes (Heinrich et al 1990), and a correlation between plasma IL-6 concentration and CRP has been noted in virus-induced fulminant hepatic failure (Sekiyama et al 1994, Izumi et al 1994). Given the small numbers of patients studied correlations between cytokines and clinical variables were not expected in the present study. Wigmore and colleagues (1998) have shown that white blood cells from patients with fulminant hepatic failure have reduced ability to produce TNF and IL-6 in vitro, which may indicate early activation in vivo with subsequent exhaustion in this condition. This, in conjunction with the effect of increased plasma concentrations of pro-inflammatory cytokines on other tissues, probably explain the marked elevation in energy expenditure in patients with paracetamol-induced fulminant hepatic failure.

## CONCLUSIONS

- 1) Energy expenditure is significantly increased in patients with paracetamol-induced fulminant hepatic failure.
- 2) The Harris-Benedict equation has low predictive value for estimating metabolic rate in patients with fulminant hepatic failure.
- 3) Fulminant hepatic failure is accompanied by a marked systemic inflammatory response and acute phase protein response which probably account for increased metabolic rate.

# THE EFFECT OF GRAFT REPERFUSION ON HAEMODYNAMICS AND GAS EXCHANGE DURING LIVER TRANSPLANTATION

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### OBJECTIVES

To describe in detail the changes in pulmonary and systemic haemodynamics, gas exchange and metabolic rate which occur after reperfusion during liver transplantation.

### BACKGROUND

In the introduction to this thesis a review of the physiological changes associated with different stages of the liver transplant procedure was made. These changes are most dramatic, and are associated with most morbidity, during and immediately following reperfusion of the donor graft. The pathophysiology of reperfusion are incompletely understood and in particular there have been no studies which document in detail the alterations in gas exchange which occur or their relationship to haemodynamic changes and acid-base balance. These are important because they may contribute to potentially fatal complications such as acute intracranial hypertension which can occur at this time. My aim in this chapter was to use indirect calorimetry to study in detail the physiological changes which occur at reperfusion.

### METHODS

#### Patients

Twenty patients undergoing orthotopic liver transplantation were prospectively studied (mean age 52, range 21 to 67). In 8 patients venovenous bypass from portal and femoral veins to axillary vein was used during the anhepatic phase. In the remaining 12 patients

the piggyback technique was used. In all of these patients a temporary portacaval shunt was constructed during the anhepatic period. Anaesthesia was maintained with a propofol/alfentanil infusion regime supplemented with midazolam. An atracurium infusion was used for muscle relaxation and the lungs were ventilated with an air/oxygen mixture using a Servo 900C ventilator. Ventilator settings were adjusted to achieve a  $\text{PaCO}_2$  of 3.5-4.5 kPa early in the operation and were not altered during the study period. All patients received dopamine at  $3\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , and aprotinin at a rate of 500,000 units per hour following a loading dose of 2 million units. Arterial, central venous, and pulmonary artery pressures were monitored continuously. Cardiac output was measured semi-continuously using a thermodilution technique (Baxter Vigilance system). Haemodynamic data were collected continuously to computer via the analogue output of the monitors. Fluids and blood products were administered as clinically indicated, and following reperfusion boluses of adrenaline were given to treat hypotension if required. No patients received bicarbonate or other alkali therapy during the study period.

### Measurements

Metabolic gas exchange was measured with the Deltatrac metabolic monitor. The accuracy of the machine was checked every 3 months by an alcohol burning test (for RQ) and a flow generator calibration. Before each use the machine was allowed to warm up for 30 minutes and was then calibrated for atmospheric pressure using an aneroid barometer. A gas calibration was carried out before each measurement against a standard mixture (95%  $\text{O}_2$ , 5%  $\text{CO}_2$ ). All data were collected each minute to computer using software supplied by the manufacturer.

In each patient an arterial blood sample was drawn as part of the routine perioperative monitoring before and approximately 30 minutes after reperfusion. Samples were processed within 5 minutes of collection using an IL BGE 1400 series analyser which was checked daily using a quality control sample. Five minute averages for all haemodynamic data and metabolic data were calculated retrospectively at the times of blood sampling in each patient. From this data the following derived variables were calculated before and

after reperfusion:

*Mixed expired CO<sub>2</sub> pressure* (PECO<sub>2</sub>) = (PB.atm.-SVP(H<sub>2</sub>O)).FECO<sub>2</sub>

(PB.atm., barometric pressure; SVP(H<sub>2</sub>O), saturated vapour pressure of water at 37°C)

*Pulmonary deadspace ratio* (VD/VT) = (PACO<sub>2</sub>-PECO<sub>2</sub>)/PACO<sub>2</sub>

(PACO<sub>2</sub>, alveolar CO<sub>2</sub> pressure, assumed to equal PaCO<sub>2</sub>)

*Alveolar ventilation* (VA) = (VCO<sub>2</sub>.95)/PACO<sub>2</sub>

*Alveolar oxygen pressure* (PAO<sub>2</sub>) = FIO<sub>2</sub> - SVP(H<sub>2</sub>O) - PACO<sub>2</sub>/RQ

*Alveolar to arterial oxygen tension gradient* (A-a gradient) = PAO<sub>2</sub> - PaO<sub>2</sub>

Differences between physiological variables before and after reperfusion were compared using Student's paired t test. The relationship between changes in physiological variables at reperfusion was investigated by calculating the Pearson product moment correlation coefficient. P<0.05 was considered statistically significant.

## RESULTS

The indications for surgery were as follows: primary biliary cirrhosis (8 patients), primary sclerosing cholangitis (3 patients), alcoholic cirrhosis (4 patients), chronic rejection of liver transplant (2 patients), and fulminant hepatic failure (3 patients). No patients suffered cardiac arrhythmias at reperfusion and there were no cases of primary graft non-function. All patients had successful transplants and were alive at one month. The mean time of blood sampling after reperfusion was 28 minutes (SD 11 mins). Continuous monitoring of metabolic gas exchange revealed increases in VO<sub>2</sub> and VCO<sub>2</sub> which consistently occurred within 2-3 minutes of graft reperfusion (figure 5.1). Changes in physiological variables at reperfusion are summarised in table 5.1.

Boluses of adrenaline were required after reperfusion to maintain arterial blood pressure in 16 patients. The maximum dose required in any patient was 0.8mg and no patients required infusions of adrenaline or other inotropic drugs. There was no correlation



between adrenaline usage and haemodynamic or gas exchange changes.

Physiological changes were compared between patients transplanted using venovenous bypass and piggyback surgical techniques. In patients transplanted with the piggyback technique the increase in  $\text{PaCO}_2$  and hydrogen ion concentration was less than with venovenous bypass (table 5.2). Changes in the other measured variables were similar.

There were significant correlations between changes in  $\text{PaCO}_2$  and  $\text{VCO}_2$  ( $r = 0.5$ ,  $P < 0.02$ ), cardiac output and  $\text{VCO}_2$  ( $r = 0.58$ ,  $P < 0.01$ ), and cardiac output and  $\text{VO}_2$  ( $r = 0.58$ ,  $P < 0.01$ )(figures 5.2 and 5.3).



Figure 5.1: Typical changes in  $\text{VCO}_2$ ,  $\text{VO}_2$ , and  $\text{PaCO}_2$  over time in an individual patient. Values are mean  $\pm$  SD.

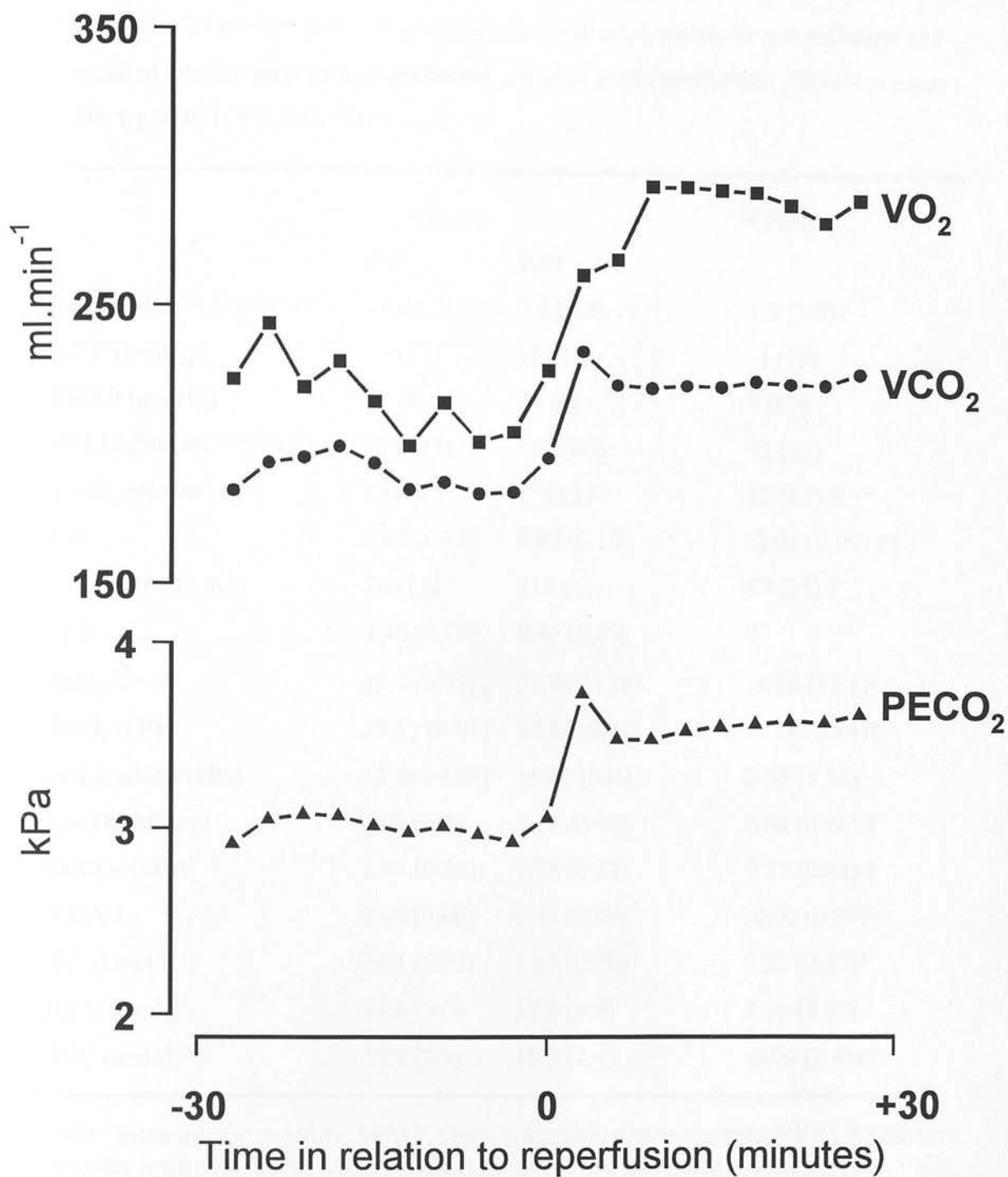


Figure 5.1: Typical example of changes in  $\text{VO}_2$ ,  $\text{VCO}_2$ , and  $\text{PECO}_2$  after reperfusion in an individual patient during constant ventilation.

TABLE 5.1: Comparison between haemodynamic variables, metabolic gas exchange and associated physiological parameters before and after graft reperfusion. All values mean (SD). †  $p < 0.001$ ; \*  $p < 0.01$ ; ††  $p < 0.02$ .

	Reperfusion		Change
	Pre	Post	
Cardiac output ( $\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ )	4.6 (1.3)	5.9 (1.5)	1.2 (1.0)†
MAP (mmHg)	74 (13)	70 (15)	-4 (15)
MPAP (mmHg)	15 (4)	24 (6)	9 (6)†
PVRI ( $\text{dyne} \cdot \text{sec} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$ )	125 (87)	137 (69)	12 (23)
VCO <sub>2</sub> ( $\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ )	138 (30)	176 (37)	38 (17) †
RQ	0.87 (0.12)	0.82 (0.10)	-0.05 (0.09) ††
VO <sub>2</sub> ( $\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ )	160 (32)	217 (46)	57 (25) †
FIO <sub>2</sub>	0.46 (0.09)	0.46 (0.09)	0
PaO <sub>2</sub> (kPa)	25.7 (6.75)	21.79 (6.38)	-3.86 (5.31)*
PAO <sub>2</sub> (kPa)	38.51 (9.01)	37.23 (9.17)	-1.28 (0.84)†
A-a gradient (kPa)	12.86 (5.99)	15.44 (8.02)	2.58 (5.58)
PaCO <sub>2</sub> (kPa)	4.40 (0.73)	5.27 (0.90)	0.88 (0.56) †
PECO <sub>2</sub> (kPa)	2.21 (0.31)	2.78 (0.37)	0.57 (0.23) †
VD/VT	0.49 (0.06)	0.46 (0.09)	-0.03 (0.05)*
VA ( $\text{l} \cdot \text{min}^{-1}$ )	3.02 (0.62)	3.23 (0.70)	0.22 (0.27)*
[H <sup>+</sup> ] ( $\text{nmol} \cdot \text{l}^{-1}$ )	44.8 (9.6)	52.8 (9.9)	8.15 (5.9)†
SBC ( $\text{mmol} \cdot \text{l}^{-1}$ )	20.8 (2.9)	19.9 (2.4)	-0.96 (1.6)††

MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PVRI, pulmonary vascular resistance index; RQ, respiratory quotient; FIO<sub>2</sub>, inspired oxygen fraction; PaO<sub>2</sub>, arterial oxygen tension; PAO<sub>2</sub>, alveolar partial pressure of oxygen; A-a gradient, alveolar to arterial oxygen tension gradient; PaCO<sub>2</sub>, arterial carbon dioxide tension; PECO<sub>2</sub>, mixed expired carbon dioxide partial pressure; VD/VT, deadspace ratio; VA, alveolar ventilation; [H<sup>+</sup>], hydrogen ion concentration; SBC, standard bicarbonate concentration.

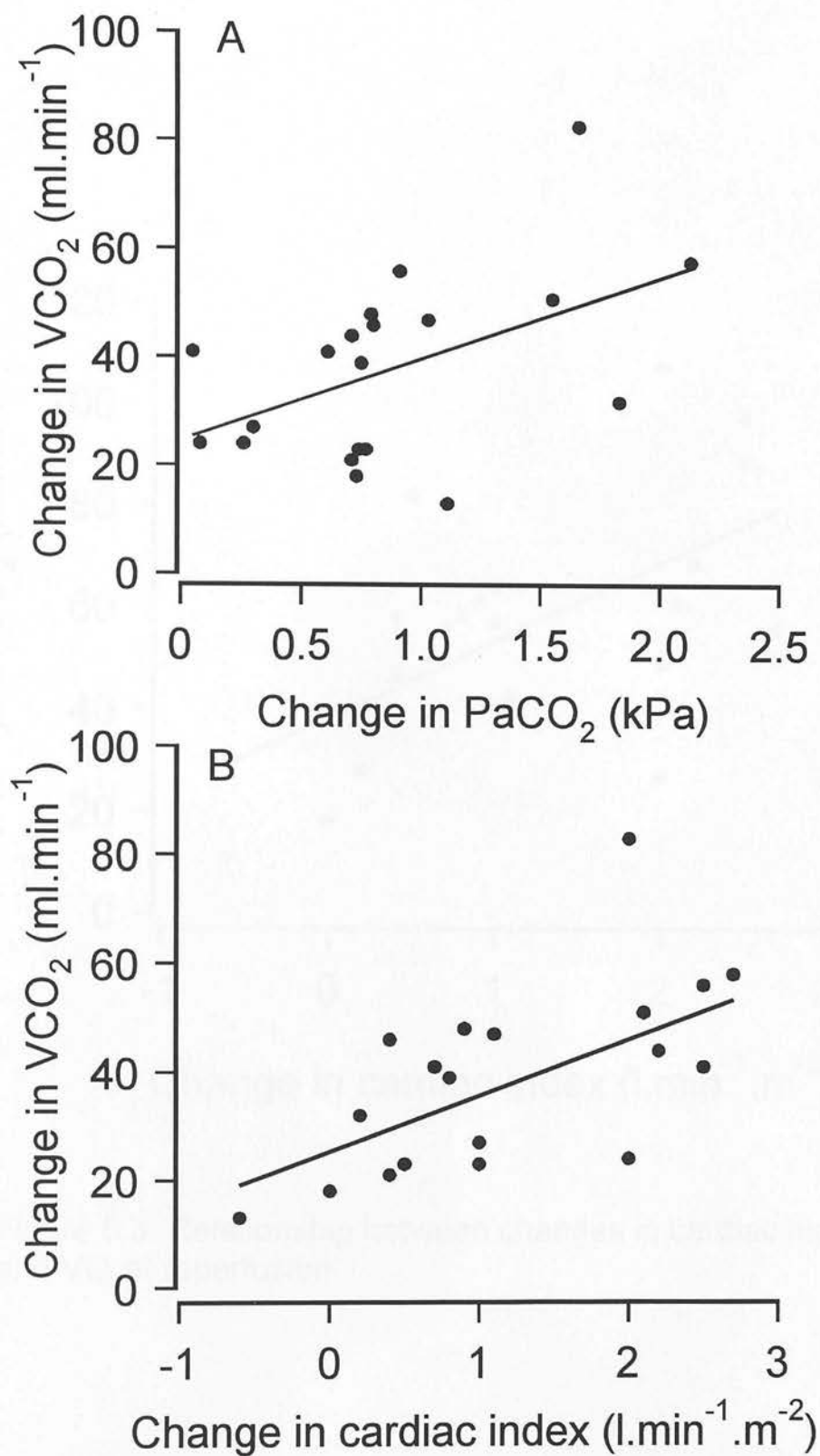


Figure 5.2. A: Relationship between changes in  $\text{PaCO}_2$  and  $\text{VCO}_2$  at reperfusion. B: Relationship between changes in cardiac index and  $\text{VCO}_2$  at reperfusion.

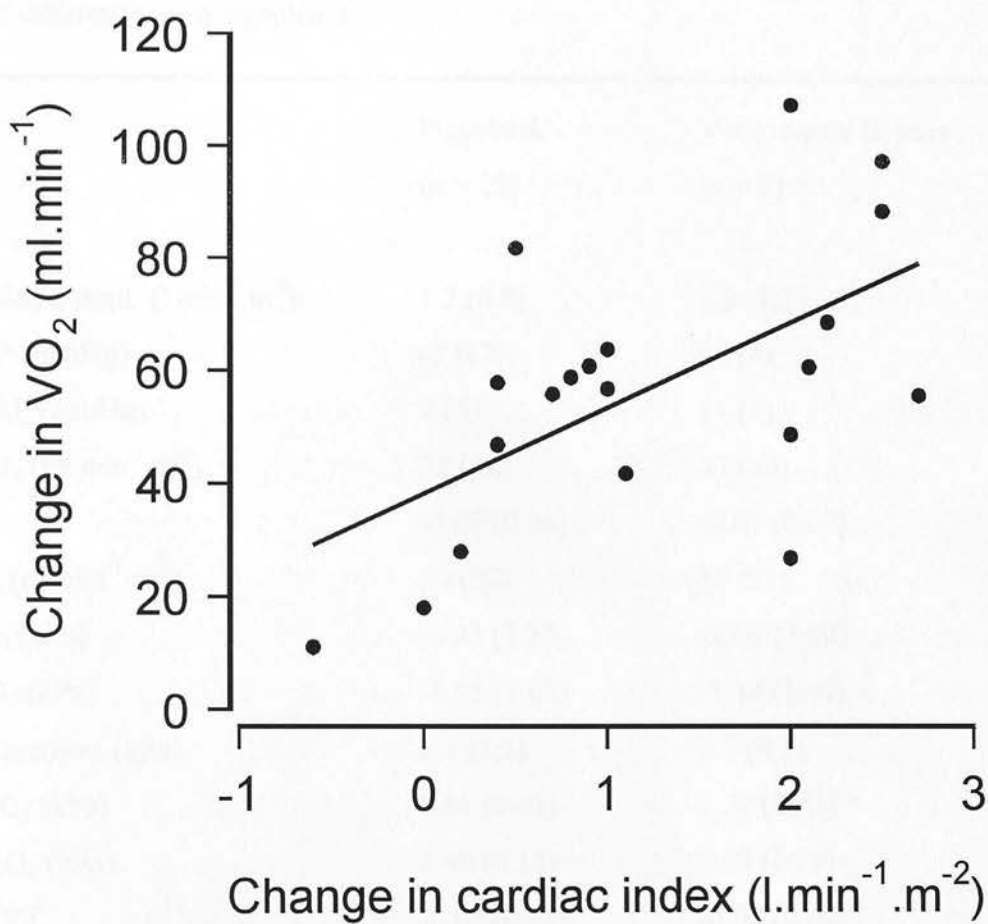


Figure 5.3: Relationship between changes in cardiac index and  $VO_2$  at reperfusion

TABLE 5.2: Comparison of physiological changes occurring at reperfusion between patients transplanted using the piggyback technique and those transplanted using venovenous bypass during the anhepatic phase. \* P<0.02 between the groups. All other differences non-significant.

	Piggyback (n = 12)	Venovenous Bypass (n = 8)
Cardiac output (l.min <sup>-1</sup> .m <sup>-2</sup> )	1.2 (0.8)	1.3 (1.2)
MAP (mmHg)	-7 (12)	1 (18)
MPAP (mmHg)	7 (6)	11 (6)
VCO <sub>2</sub> (ml.min <sup>-1</sup> .m <sup>-2</sup> )	32 (12)	47 (20)
RQ	-0.07 (0.08)	-0.01 (0.09)
VO <sub>2</sub> (ml.min <sup>-1</sup> .m <sup>-2</sup> )	56 (20)	59 (33)
PaO <sub>2</sub> (kPa)	-3.33 (3.35)	-4.66 (7.60)
PAO <sub>2</sub> (kPa)	-1.25 (0.69)	-1.34 (1.07)
A-a gradient (kPa)	2.1 (3.3)	3.3 (8.1)
PaCO <sub>2</sub> (kPa)	0.61 (0.41)	1.27 (0.53) *
PECO <sub>2</sub> (kPa)	0.48 (0.13)	0.69 (0.29)
VD/VT	-0.04 (0.13)	-0.02 (0.04)
VA (l.min <sup>-1</sup> )	204 (271)	233 (277)
H <sup>+</sup> concentration (nmol.l <sup>-1</sup> )	5.59 (5.50)	11.74 (4.60) *
Standard bicarbonate (mmol.l <sup>-1</sup> )	-0.8 (1.4)	-1.3 (1.07)



## DISCUSSION

The principal finding in this chapter is that reperfusion of the donor graft during liver transplantation is associated with dramatic changes in gas exchange and metabolic rate. Clinically significant increases in  $\text{VO}_2$  and  $\text{VCO}_2$  occurred within minutes of removing the vascular clamps and restoring blood supply to the graft. These changes were associated with the well-established observation that cardiac output and pulmonary artery pressure increase at reperfusion and systemic vascular resistance decreases (Aggarwal et al 1987, Estrin et al 1989, Webster et al 1994).

The accuracy of physiological measurements made during a period of rapid change was an important consideration in considering these findings. The validity of thermodilution measurements of cardiac output is decreased by rapid changes or fluctuations in blood temperature, and rapid infusion of intravenous fluids both of which occur frequently at the time of reperfusion (Nishikawa et al 1993). Data were not analysed in the immediate post-reperfusion period, and an automated semicontinuous method of determining cardiac output was used which has the advantage of eliminating operator error and averaging multiple data points. Bottiger et al (1997) showed that the agreement between this method and conventional bolus thermodilution was good during liver transplantation if about 30 minutes had elapsed from reperfusion. It is therefore unlikely that large errors occurred in measurements of cardiac output in the patients. As discussed in the previous chapters the accuracy of the Deltatrac metabolic monitor is reduced in the presence of a high or fluctuating  $\text{FIO}_2$ , anaesthetic gases, or the presence of gas leaks in the circuit, but these were not relevant in this study. The assumption that the patient is at steady state was a further consideration. Ventilation was not altered during the study period, but the significant changes in cardiac output, acid-base status, and deadspace ratio which were observed all represent disruptions to steady state which may have influenced the validity of  $\text{VO}_2$  estimations. Inaccuracy attributable to these factors should decline exponentially with time as a new equilibrium is established after reperfusion. The data indicate that devices which assume the presence of a steady state when determining  $\text{VO}_2$  following graft reperfusion may be inaccurate until an equilibrium has been re-established. The

time required for this to occur is unknown and is likely to vary between patients. Following changes in ventilation the majority of this process occurs within 20 minutes (Nunn 1977, Taskar et al 1995) and it is likely that errors attributable to haemodynamic, acid-base, and deadspace changes were small 30 minutes after reperfusion assuming the patients were otherwise stable. This conjecture was supported by the observation that  $\text{VO}_2$  plateaued within 5-10 minutes, and then did not fluctuate significantly in the majority of patients.

The increase in  $\text{PaCO}_2$  which occurred has several explanations. Firstly, increased aerobic metabolism by the graft resulted in an increase in  $\text{CO}_2$  production which was not compensated for by increased ventilation, which intentionally remained unchanged. Secondly, the small decrease in standard bicarbonate concentration indicated an acute metabolic acidosis which probably resulted from the release of an acid load from the graft and other ischaemic tissues. Welte et al (1996) found that gastric intramucosal pH decreased during the anhepatic phase of liver transplantation which was consistent with the presence of gut ischaemia, and this resolved following reperfusion. In the patients in the present study there was no correlation between the changes in standard bicarbonate or hydrogen ion concentration and  $\text{PaCO}_2$  which may indicate that buffering of the acid load was not a major determinant of the  $\text{PaCO}_2$  change. Impaired  $\text{CO}_2$  elimination might have contributed to the increase in  $\text{PaCO}_2$ , but despite constant ventilator settings a small but statistically significant decrease in deadspace ratio and an increase in alveolar ventilation were observed, which would augment rather than impair  $\text{CO}_2$  elimination. The most likely explanation for these changes was increased pulmonary perfusion and a decrease in the  $\text{V}/\text{Q}$  ratios of non-dependent alveoli, attributable to increased pulmonary artery pressure and cardiac output.

The observed increase in  $\text{VCO}_2$  following reperfusion correlated with the increase in  $\text{PaCO}_2$ . This association was expected under conditions of constant ventilation where, in the absence of severe pulmonary disease, alveolar and arterial  $\text{pCO}_2$  are virtually identical (Nunn 1977). The results also indicate that altered pulmonary blood flow

may be an important determinant of  $\text{VCO}_2$  because a correlation was found between changes in cardiac output and  $\text{VCO}_2$ . This observation is consistent with those made by Shibutani et al (1994) in patients undergoing aortic aneurysm surgery in whom decreases in  $\text{VCO}_2$  correlated strongly with decreases in cardiac output.

An increase in arterial  $\text{CO}_2$  tension causes vasodilatation (Nunn 1977). In patients with acute respiratory distress syndrome Thorens et al (1996) showed that acute hypercapnia, induced over 30-60 minutes by a reduction in minute ventilation, increased cardiac output and pulmonary artery pressure and decreased systemic vascular resistance. Although many factors may be important, the similarity between these changes and those occurring in patients following graft reperfusion suggest that altered  $\text{CO}_2$  tension may contribute to the haemodynamic changes which occur following reperfusion during liver transplantation.

A possible clinical relevance of altered  $\text{CO}_2$  metabolism relates to cerebral blood flow in patients with abnormal cerebral autoregulation or intracranial hypertension. Neurological complications are common following reperfusion in patients undergoing liver transplantation for fulminant hepatic failure, but cerebral oedema can also complicate chronic liver disease (Donovan et al 1998). The exact aetiology of the acute increases in intracranial pressure which occur following reperfusion is unclear and is probably multifactorial, but cerebral vasodilatation in response to increased arterial  $\text{CO}_2$  tension is a possible contributing factor. Gunning and colleagues (1990) noted the similarity between the acute intracranial hypertension which can occur following deflation of limb tourniquets in at risk patients and the changes which occur at reperfusion, when substances from previously ischaemic tissues are released into the circulation including a significant acid load. The cerebrovascular response to acute hypercapnia in patients with normal autoregulation is extremely rapid (<10 seconds)(Poulin et al 1996). An increase in middle cerebral artery blood flow velocity, measured by transcranial Doppler, occurs following reperfusion in patients with chronic liver disease and can be attenuated, but not completely abolished by hyperventilation prior to reperfusion (Doblar et al 1995). The data indicate that an

increase in minute ventilation is advisable prior to reperfusion in order to minimise the risk of CO<sub>2</sub>-induced cerebral vasodilatation in patients at risk of cerebral complications.

PaCO<sub>2</sub> and hydrogen ion concentration increased less in patients transplanted using the piggyback technique although changes in standard bicarbonate concentration were not statistically significant. This indicates that the acidaemia following reperfusion was greater when venovenous bypass was used although buffering resulted in no difference in systemic acidosis. Steib et al (1997) found cardiac output and oxygen delivery were higher during the anhepatic phase of transplantation with the piggyback technique in comparison with venovenous bypass. Better organ perfusion, particularly of splanchnic tissues, during the anhepatic phase of transplantation may account for the smaller acid load released into the systemic circulation at reperfusion with the piggyback technique. This hypothesis is explored in the next chapter and may be clinically important if acidaemia or other ischaemic metabolites contribute to cardiovascular or neurological instability.

There was a relationship between changes in cardiac output and VO<sub>2</sub> following reperfusion. There are two possible explanations for this: firstly, VO<sub>2</sub> may be supply-dependent at this time, particularly if the increase in cardiac output improves oxygen delivery to tissues which were ischaemic during the anhepatic period (Steib et al 1987). Alternatively, metabolism by the new liver, resulting in increased oxygen demand, may be the major determinant of cardiac output and therefore oxygen delivery. Previous studies have suggested that the change in VO<sub>2</sub> at reperfusion is a clinically useful measure of graft function (Svensson et al 1989, Steltzer et al 1992, Gubernatis et al 1989). However, several factors could influence VO<sub>2</sub> at this time. In particular, if the change in VO<sub>2</sub> is in part attributable to factors other than metabolism of the graft, such as adrenaline usage and oxygen debt in splanchnic tissues incurred during the anhepatic phase, the sensitivity and specificity of this test are unlikely to be high. This may explain why some authors have observed a large increase in VO<sub>2</sub> in patients in whom primary liver non-function occurred (Albaladejo et al 1994).

In most patients the increase in  $\text{VO}_2$  was slightly larger than the increase in  $\text{VCO}_2$  and this was reflected by a small but statistically significant decrease in the RQ. A similar observation was made by Svensson et al (1989) and it is possible that this occurred because of altered substrate utilisation at the tissue level such as restoration of hepatic lipolysis. An alternative explanation is that the excess oxygen consumption was due to free radical formation, which consumes oxygen without the production of  $\text{CO}_2$ . Free radical production has been demonstrated after reperfusion, may continue for up to 24 hours, and has been implicated in the process of reperfusion injury (Bzeizi et al 1993, 1997). Indirect evidence that this occurs also comes from work demonstrating acute depletion of plasma antioxidants following reperfusion (Goode et al 1994).

Despite significant changes in pulmonary artery pressure and blood flow A-a oxygen tension gradient, a measure of physiological shunt, did not change in the majority of patients. Small decreases in  $\text{PAO}_2$  and  $\text{PaO}_2$  were observed which were largely explained by the increase in  $\text{PACO}_2$  and which were not clinically important in the patients in this study. These changes might become relevant in patients with limited physiological reserve because of coexisting pulmonary disease, which occurs in both chronic and acute liver disease (Krowka et al 1996, Baudouin et al 1995). However, the data indicate that the routine use of high inspired oxygen fractions at reperfusion, which is frequently recommended, is unnecessary. Indeed, the use of high inspired oxygen fractions increases lung atelectasis during anaesthesia (Rothen et al 1995).

## CONCLUSIONS.

- 1) Increases in  $\text{VO}_2$ ,  $\text{VCO}_2$ , and  $\text{PaCO}_2$  occur following reperfusion because of oxygen uptake by the new liver, and the perfusion of tissues which were ischaemic during the anhepatic period.
- 2) The degree of acidaemia following reperfusion is greater when venovenous bypass is used in comparison with the piggyback technique. This is associated with a greater increase in  $\text{PaCO}_2$  and may be relevant in patients with cardiovascular or

neurological instability.

- 3) During routine liver transplantation the effect of reperfusion on arterial oxygen tension is not clinically significant.
- 4) Carbon dioxide elimination is augmented by increased pulmonary perfusion and a decrease in physiological deadspace. However, an increase in metabolic rate and buffering of the acid load released in association with reperfusion make it advisable to routinely increase minute ventilation at this time.



### **OXYGEN TRANSPORT AND UPTAKE DURING LIVER TRANSPLANTATION: A COMPARISON BETWEEN VENOVENOUS BYPASS AND PIGGYBACK SURGICAL TECHNIQUES.**

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#### **OBJECTIVES**

- 1) To compare cardiac output during liver transplantation, using either venovenous bypass or the piggyback technique, using a semicontinuous method of measurement.
- 2) To compare whole body oxygen consumption, carbon dioxide elimination, and indices of tissue hypoxia with each surgical technique using indirect calorimetry to avoid the measurement errors associated with the reverse Fick method.

#### **INTRODUCTION**

In the introduction to this thesis the different surgical techniques in use for performing liver transplantation were described. In particular the possible benefits of the piggyback technique for maintaining haemodynamic stability and tissue oxygenation during the anhepatic period were discussed. Other than anecdotal reports and retrospective series of patients there are few studies which compare the 2 techniques. Steib et al (1997) found that cardiac output and oxygen delivery were better maintained during the anhepatic period when the piggyback technique was compared with venovenous bypass, but from their data it is not clear whether this was associated with improved oxygen uptake or reduced tissue ischaemia. The interpretation of this and other previous work is not straightforward because conclusions were based on small numbers of data points, and the reverse Fick method was used to calculate oxygen consumption. In chapter 3 of this thesis it has been demonstrated that the reverse Fick method is inaccurate in patients in whom the cardiac output and mixed venous oxygen saturations are high, as is typical in many patients undergoing liver transplantation. In addition, when the relationship between oxygen delivery and

consumption is examined during periods of change mathematical coupling has the potential to cause artificial correlations. In this chapter a prospective observational study is described in which the piggyback and venovenous bypass techniques are compared in relation to cardiac output and gas exchange data. The methodology attempts to eliminate or reduce the effect of factors which confuse the interpretation of oxygen kinetics studies.

## **METHODS**

### **Patients and techniques:**

Sixteen patients undergoing liver transplantation were studied prospectively. In 8 patients venovenous bypass was established from the femoral and portal veins to the axillary vein prior to cross-clamping the inferior vena cava above and below the hepatic veins. During the anhepatic period bypass flow rate was increased to the highest achievable value using a centrifugal pump. In the remaining 8 patients the piggyback technique was used: inferior vena caval flow was preserved throughout the anhepatic period with the only interference to blood flow being the application of a side-biting clamp to the vena cava at the level of the hepatic veins. In 6 patients a temporary portacaval shunt was constructed prior to recipient hepatectomy; in the other 2 patients, a test period of portal vein cross-clamping suggested adequate collateral circulation and the portal vein remained cross-clamped during the anhepatic period. The choice of technique was made by the surgeon. In all patients the grafted liver was reperfused via the portal vein. The groups were comparable for age, diagnosis and Childs-Pugh scores (table 6.1).

The same total intravenous anaesthetic technique was used in all cases using infusions of propofol, midazolam, and alfentanil (see previous chapter). An atracurium infusion provided full muscle relaxation and the lungs were ventilated through a Servo 900C ventilator using an air-oxygen mixture. In the early stages of the procedure the minute volume and the  $\text{FIO}_2$  were adjusted to achieve an arterial carbon dioxide tension

(PaCO<sub>2</sub>) of 4-5.5kPa and an arterial oxygen tension (PaO<sub>2</sub>) of 15-25kPa. Thereafter changes in ventilator setting were made only if clinically indicated. All patients received a dopamine infusion at a rate of 2µg.kg<sup>-1</sup>.min<sup>-1</sup> throughout the procedure, and aprotinin at a rate of 0.5 million units per hour following a loading dose of 2 million units.

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TABLE 6.1: Demographic data for the patients studied. Mean (range).

	Piggyback	Venovenous bypass
Age	53 (45-60)	55 (44-67)
Diagnosis		
Primary biliary cirrhosis	4	3
Alcoholic liver disease	2	1
Primary Sclerosing Cholangitis	1	2
Non A, non B, non C hepatitis	1	
Chronic rejection		2
Child's Grade	2A, 3B, 3C	2A, 4B, 2C
Sex (F/M)	4/4	5/3

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Arterial and central venous pressures were monitored continuously. Cardiac output was measured semicontinuously with a thermodilution technique (Baxter Vigilance system). All haemodynamic data were recorded to computer each minute from the monitors using an analogue/digital converter. Every 30 minutes arterial blood gas analysis was carried out using an IL BGE 1400 series analyser which was checked daily using a quality control sample, and whole blood lactate measured using a YSI 2300 Stat Plus analyser.

The Deltatrac metabolic monitor was used to measure oxygen consumption and carbon dioxide elimination. The accuracy of the machine was checked every 3 months

by an alcohol burning test. Before each use the machine was calibrated for atmospheric pressure using an aneroid barometer and a gas calibration was carried out using a standard mixture (95% O<sub>2</sub>, 5% CO<sub>2</sub>). Measured gas volumes are expressed at standard temperature and pressure.

Identical methods of heat preservation were employed in all patients. A heating blanket was placed under the patients and over the lower limbs (Cincinnati Sub-zero Norm-O-Temp, CSZ Products Inc, Cincinnati, Ohio). After induction of anaesthesia the limbs were wrapped in gamgee and polythene. All intravenous fluids and blood products were administered at 37°C using a blood warmer/rapid infusion system (Level 1, Level 1 technologies Inc., Rockland, MA, USA).

### *Data Collection*

All cardiac output and gas exchange data were recorded each minute to computer throughout the procedure. Retrospectively the mean for these variables was calculated for 4 time periods:

- I (*Baseline*): The 20 minute period immediately prior to ligation of the hepatic artery.
- II (*Anhepatic*): The mean of data for the *entire* anhepatic period.
- III (*Post reperfusion 30*): The mean of data for a 20 minute period starting 30 minutes after vascular reperfusion of the graft.
- IV (*Post reperfusion 90*): The mean of the 20 minute period from 90 to 110 minutes after graft reperfusion.

Pulmonary artery blood temperature was recorded during the baseline period, immediately prior to reperfusion, and at 90 minutes post-reperfusion. Blood samples were analysed at the following time points:

- Time point A: during time period I.
- Time point B: during the 10 minutes prior to reperfusion (end anhepatic).
- Time point C: during time period III.
- Time point D: during time period IV.

Data were compared using non parametric tests. As multiple tests were performed Bonferroni's correction was applied as appropriate. Correlations between pooled data were investigated by calculating the product moment correlation coefficient.

## RESULTS

All patients had functioning grafts and were alive at 3 months following surgery. In one patient in the venovenous bypass group, bypass was abandoned after 20 minutes because of problems with the portal venous flow. In this patient the procedure was completed without bypass. In the remaining 7 patients the mean bypass flow was  $2.1 \text{ l.min}^{-1}$  (SD 0.7, range 1.3-3.0  $\text{l.min}^{-1}$ ). There were no significant differences in gas exchange, cardiac output, or acid-base variables between the groups during the baseline period (table 6.2). The mean duration of the anhepatic period was significantly shorter in the piggyback group (piggyback group median 50 (range 44-196) minutes; venovenous bypass group 77 (69-127) minutes,  $P < 0.02$ ).

Data for median  $\text{VO}_2$ ,  $\text{VCO}_2$ , and cardiac index for the groups for the 4 time periods are illustrated in figure 6.2 and table 6.2. Individual data for  $\text{VO}_2$  are illustrated in figure 6.1. Analysis *within* groups indicated that  $\text{VO}_2$  decreased during the anhepatic phase in both groups and increased following reperfusion (table 6.2). In the venovenovenous bypass group a further increase in  $\text{VO}_2$  occurred between 30 and 90 minutes post-reperfusion;  $\text{VO}_2$  plateaued during this period in the piggyback group. A significant increase in  $\text{VCO}_2$  occurred in both groups following reperfusion. Cardiac index decreased during the anhepatic period in the venovenous bypass group, but did not change significantly in the piggyback group. Plotting changes *between* the groups indicated that all 3 variables decreased more during the anhepatic period in the group in which venovenous bypass was used, with differences persisting following reperfusion (figure 6.2). Statistical analysis of these differences was done by comparing changes in the physiological variables between the baseline and anhepatic periods, and between the anhepatic and post reperfusion periods. Bonferroni's correction for multiple tests was applied to these analyses.

Between the baseline and anhepatic periods decreases in  $\text{VO}_2$  and cardiac index were significantly greater in the venovenous bypass group (figure 6.3). The range of changes in cardiac output was wider in the venovenous bypass group. A trend towards a greater decrease in  $\text{VCO}_2$  was observed which was not statistically significant. For acid-base variables the only significant difference was a greater increase in  $\text{H}^+$  concentration in the venovenous bypass group (table 6.3).

At reperfusion there were no significant differences between the groups for changes in any of the gas exchange or acid-base variables (table 6.4).

Pulmonary artery blood temperature was similar for the 2 groups at the baseline time point. Core temperature was significantly lower in the venovenous bypass group both immediately before reperfusion and at 90 minutes after reperfusion. This occurred because of a more significant decrease in temperature in the venovenous bypass group during the anhepatic period (table 6.5).

In order to explore further the relationship between changes in cardiac output, temperature,  $\text{VO}_2$  and  $\text{VCO}_2$  during the anhepatic period data from all 16 patients were pooled. A correlation was found between changes from the baseline to the anhepatic period in  $\text{VO}_2$  and cardiac index, and changes in  $\text{VO}_2$  and temperature (Table 6.6).



Table 6.2: Median (1<sup>st</sup>, 3<sup>rd</sup> quartile) values for cardiorespiratory and acid-base variables for each group at each time point/period. No significant differences between groups at baseline for any variable. *Within group* comparison: † P<0.05 II/B vs I/A; †† P<0.05 III/C vs II/B; ††† P<0.05 IV/D vs III/C.

		Time Period/Point			
		I or A	II or B	III or C	IV or D
CI L.min <sup>-1</sup> .min <sup>-1</sup>	Piggyback	5.8(4.8,6.6)	5.5(4.5,6.6)	6.3(5.1,6.8)	5.8(4.7,6.7)
	Bypass	5.4(4.7,6.0)	4.0(3.7,4.5)†	4.8(4.3,5.7)††	5.6(4.7,6.3)
VO <sub>2</sub> (ml.min <sup>-1</sup> )	Piggyback	184(163,231)	172(152,207)†	242(225,266)††	238(211,272)
	Bypass	182(167,240)	132(129,172)†	193(163,217)††	213(180,236)†††
VCO <sub>2</sub> (ml.min <sup>-1</sup> )	Piggyback	167(149,175)	163(149,175)	185(174,225)††	211(181,228)
	Bypass	156(126,184)	126(116,140)	152(139,170)††	178(144,191)
Lactate (mmol.L <sup>-1</sup> )	Piggyback	0.95(0.72,1.14)	1.88(1.75,1.96)†	2.52(2.13,2.81)††	1.80(1.69,2.23)†††
	Bypass	1.25(0.73,1.68)	2.37(1.40,2.70)†	3.39(2.69,3.54)††	3.02(2.50,3.38)
SBC (mmol.L <sup>-1</sup> )	Piggyback	22.45(21.35,24.30)	22.15(21.20,23.25)	19.95(18.85,21.58)††	22.30(20.25,24.15)
	Bypass	23.10(21.25,24.53)	20.50(18.78,21.83)	18.25(16.73,20.85)	20.20(19.88,22.43)†††
PaCO <sub>2</sub> (kPa)	Piggyback	5.06(4.51,5.23)	4.69(4.08,5.03)	5.54(4.77,5.68)††	5.59(5.22,5.96)
	Bypass	4.98(4.40,5.32)	4.28(3.91,5.19)	5.96(5.14,6.28)††	5.40(5.01,5.91)
H <sup>+</sup> (nmol.L <sup>-1</sup> )	Piggyback	44.75(42.00,47.95)	42.40(39.66,46.88)	51.00(46.88,56.03)††	49.70(43.75,54.00)
	Bypass	39.75(38.83,49.28)	43.50(41.40,49.38)	58.85(54.78,62.20)††	51.80(47.03,57.68)

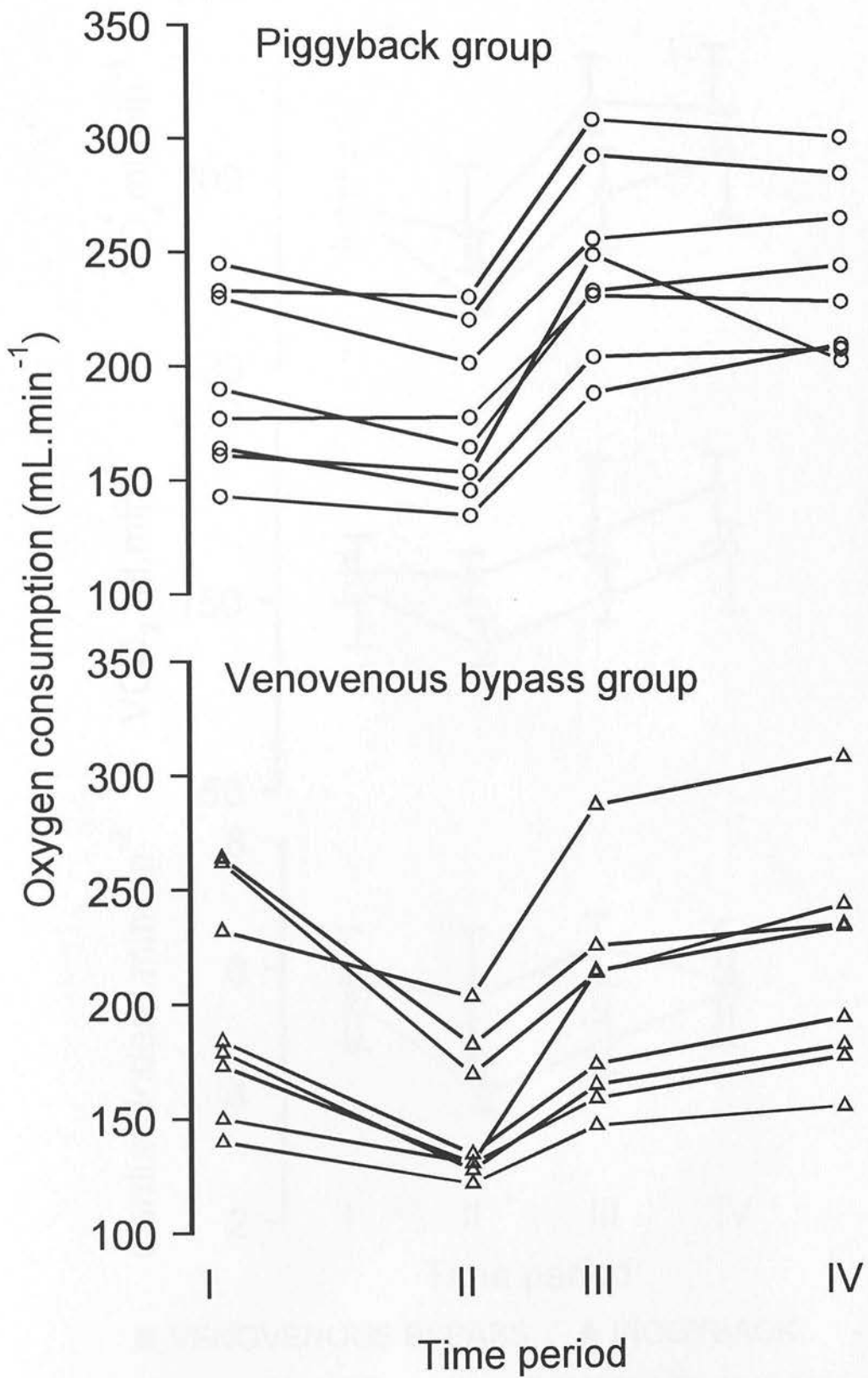


Figure 6.1: Individual data for  $\text{VO}_2$  during each time period for the two groups

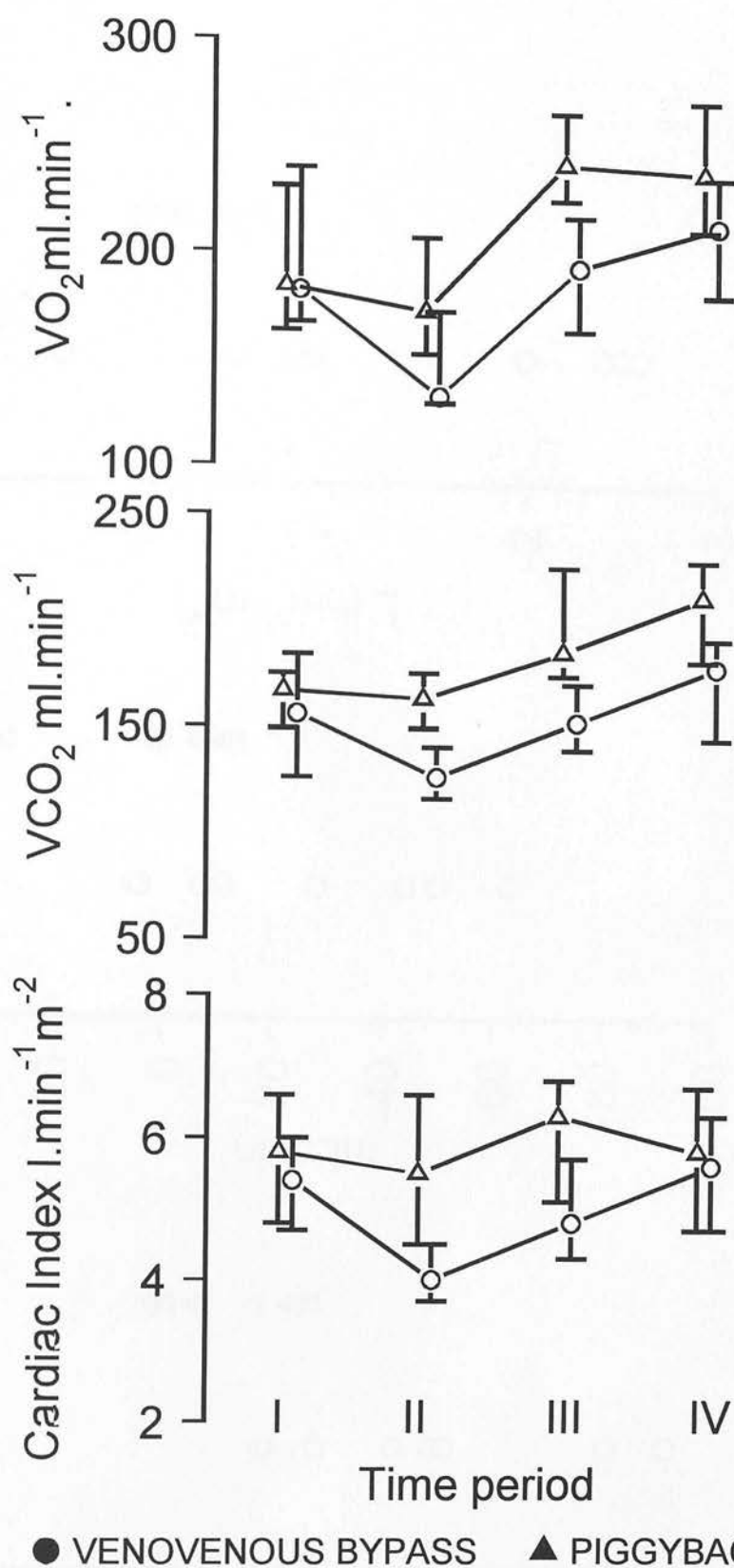


Figure 6.2:  $VO_2$ ,  $VCO_2$ , and cardiac index for each time period for the groups. All values median (1st, 3rd quartile). Statistical analysis *within* groups in table 6.3, and *between* groups in figure 6.3 and table 6.5.

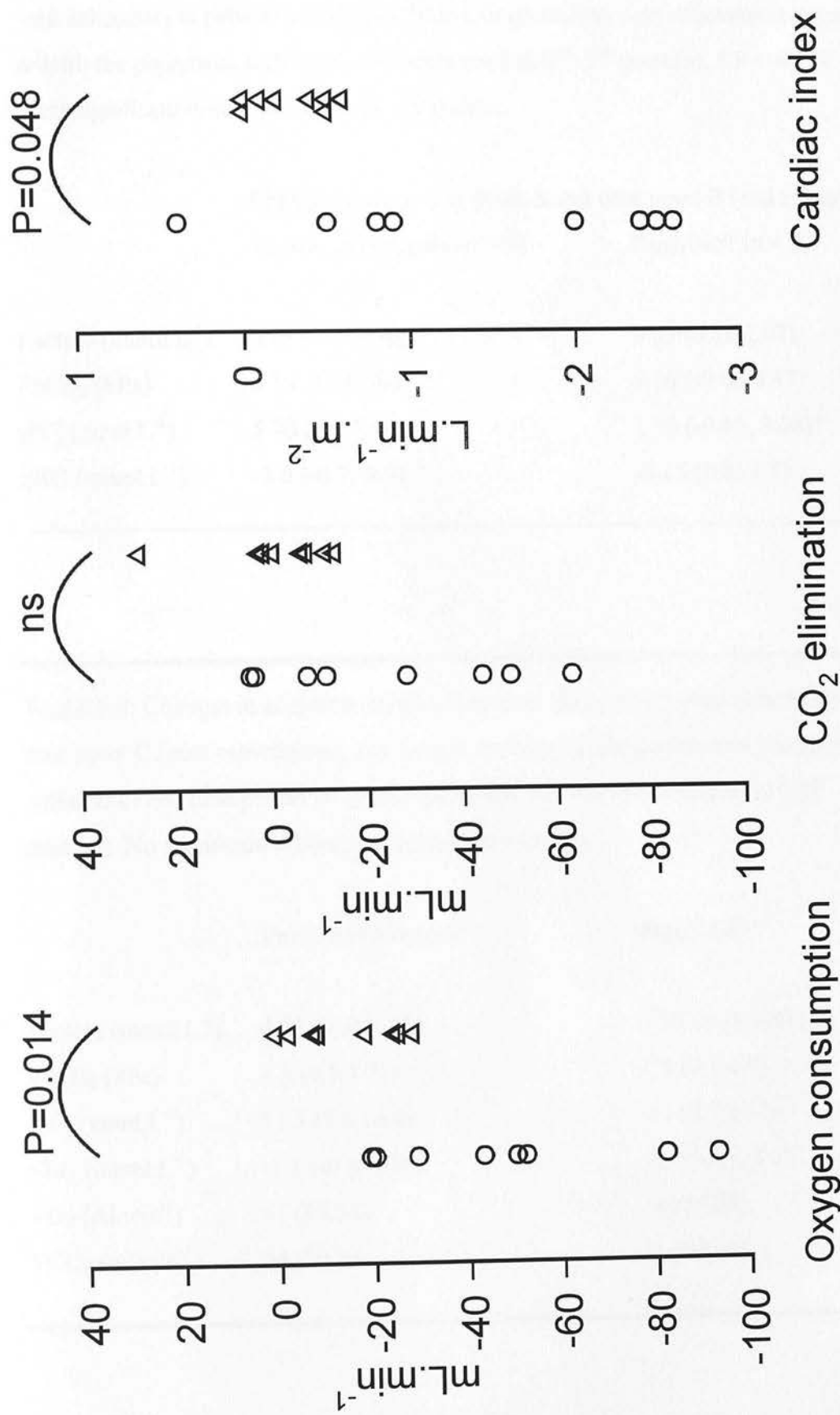


Figure 6.3: Comparison of changes in  $\text{VO}_2$ ,  $\text{VCO}_2$ , and cardiac index from the baseline to anhepatic time periods between the bypass (circles) and piggyback (triangles) groups.

TABLE 6.3: Changes in acid-base variables from timepoint A (baseline) to timepoint B (end anhepatic) in patients undergoing liver transplantation with venovenous bypass or with the piggyback technique. All values median (1<sup>st</sup>, 3<sup>rd</sup> quartile). † P = 0.028. No other significant differences between the groups.

	Change between time point A and time point B (end anhepatic)	
	Venovenous bypass (n = 8)	Piggyback (n = 8)
Lactate (mmol.L <sup>-1</sup> )	0.87 (0.49,1.28)	0.83 (0.70,1.07)
PaCO <sub>2</sub> (kPa)	0.1 (-0.2,0.70)	0.26 (-0.01,0.47)
[H <sup>+</sup> ] (nmol.L <sup>-1</sup> )	5.70 (3.1,7.90)	1.75 (-0.45, 3.28)†
SBC (mmol.L <sup>-1</sup> )	-2.0 (-0.7,-3.7)	-0.15 (0.8,-1.5)

TABLE 6.4: Changes in acid-base variables between time point B (end anhepatic) and time point C (post reperfusion), and for gas exchange variables between time period II (anhepatic) and time period III (post reperfusion 30). All values median (1<sup>st</sup>, 3<sup>rd</sup> quartile). No significant differences between the groups.

	Venovenous bypass	Piggyback
Lactate (mmol.L <sup>-1</sup> )	0.96 (0.56,1.22)	0.77 (0.44,0.91)
PaCO <sub>2</sub> (kPa)	1.3 (0.8,1.7)	0.8 (0.3,1.0)
[H <sup>+</sup> ] (nmol.L <sup>-1</sup> )	11.3 (7.6,16.0)	9.1 (4.1,10.2)
SBC (mmol.L <sup>-1</sup> )	-1.1 (-0.6,-1.9)	-1.7 (-1.1,-2.7)
VO <sub>2</sub> (ml.min <sup>-1</sup> )	41 (35,54)	64 (55,75)
VCO <sub>2</sub> (ml.min <sup>-1</sup> )	24 (20,33)	26 (23,36)

TABLE 6.5: Comparison between blood temperature during liver transplantation for patients in the venovenous bypass and piggyback groups. All values median (1<sup>st</sup>, 3<sup>rd</sup> quartile).

	Temperature (°C)		
	Venovenous Bypass	Piggyback	
Baseline	36.2 (35.8,37.0)	36.6 (36.1,37.1)	ns
Pre-reperfusion	35.5 (34.9,36.1)	36.9 (36.6,37.0)	P=0.027
Post-reperfusion	36.6 (35.9,37.1)	37.7 (37.3, 38.2)	P=0.047

TABLE 6.6: Correlations between changes in VO<sub>2</sub>, VCO<sub>2</sub>, cardiac index, and temperature between the baseline and anhepatic periods using data from all 16 patients studied.

Variables	Correlation Coefficient (r)	P value
ΔVO <sub>2</sub> vs Δtemperature	0.67	P<0.01
ΔVO <sub>2</sub> vs Δcardiac index	0.63	P<0.01
ΔVCO <sub>2</sub> vs Δtemperature	0.67	P<0.01
ΔVCO <sub>2</sub> vs Δcardiac index	0.40	ns
Δcardiac index vs Δtemperature	0.50	P=0.05



## DISCUSSION

The principal finding of this study was that cardiac output and  $\text{VO}_2$  decreased less during the anhepatic period of liver transplantation when the piggyback technique was used in comparison with venovenous bypass. The use of the continuous cardiac output computer enabled many data points to be collected and averaged for each of the study time periods. Previous studies during liver transplantation have used intermittent thermodilution measurements to collect cardiac output data. As cardiac output may change rapidly during liver transplantation, as a result of acute alterations in venous return from surgical manipulation or blood loss, "snapshots in time" are potentially subject to considerable inaccuracy. Bottiger and colleagues (1997) has shown that continuous cardiac output measurements agree closely with intermittent thermodilution during liver transplantation except in the immediate post reperfusion period. In the present study the averaging of large numbers of data should have made comparisons between patients more meaningful. The limitations of the Deltatrac metabolic monitor for measuring gas exchange in ventilated patients, and during liver transplantation, have been discussed in previous chapters. Although measurement errors can potentially occur it is likely that these are considerably smaller in this setting than with the reverse Fick method which would also introduce the potential for mathematical coupling.

This was an observational study which was not prospectively randomised. The surgical technique used in each patient was decided at the time of surgery by the surgeon. Patients were reasonably matched for diagnosis, Child's Pugh score, and baseline physiological status. In view of the relatively small numbers of patients examined it is possible that differences between the groups other than the surgical technique employed, or bias attributable to the surgeon, may have influenced results.

The data confirm the findings of previous studies, which used intermittent measurements, that cardiac output is well maintained during the anhepatic phase with the piggyback technique (Figueras et al 1993, Belghiti et al 1995, Steib et al 1997). The data are also consistent with studies which documented a decrease in cardiac

output during the anhepatic phase despite the use of venovenous bypass (Kang et al 1989, Shaw et al 1984, Cheema et al 1995). The decrease in cardiac output which occurs using venovenous bypass is dependent on the degree of fluid loading and bypass flow rates (Kindscher et al 1993, Steib et al 1997). Excessive fluid loading is usually avoided because of the risk of fluid overload following reperfusion, and bypass flow rates are frequently limited by the size and position of vascular cannulae. Consistent with these problems were the more predictable changes in cardiac output which occurred in the piggyback group in comparison with the venovenous bypass group. The only previous prospective comparison of the 2 techniques had similar findings, with a mean difference in cardiac index during the anhepatic period of  $1.1 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  based on 2 data points measured using intermittent thermodilution (Steib et al 1997).

Several factors are likely to contribute to the decrease in  $\text{VO}_2$  which occurs during the anhepatic phase of liver transplantation. The physical removal of the liver, which in health accounts for approximately 25% of basal metabolic rate, results in a decrease in energy expenditure and therefore  $\text{VO}_2$  by the body (Svensson et al 1989). Within groups analysis indicated a decrease in  $\text{VO}_2$  during the anhepatic period in both groups, but the magnitude of the decrease was significantly greater in the patients in whom venovenous bypass was used. The groups were comparable for diagnoses and severity of liver disease and it is unlikely that differences in hepatic oxygen uptake explained the differences observed between the 2 surgical techniques.

Given the differences in cardiac output and therefore global  $\text{DO}_2$  between the groups it is possible that  $\text{VO}_2$  differed because it was supply limited during the anhepatic period. In a study using gastric tonometry during liver transplantation, in which venovenous bypass was employed, Welte et al (1996) found evidence of gastric mucosal acidosis during the anhepatic period which they attributed to reduced splanchnic perfusion, and which resolved following reperfusion. Inadequate oxygen delivery to tissues may result from either inadequate perfusion pressure or flow and may occur more frequently with venovenous bypass. Anaerobic metabolism results in

an accumulation of acid and lactate. In the present study there were no statistically significant differences between the groups in lactate concentrations or acidosis prior to reperfusion although patients in the venovenous bypass group were more acidaemic. Following reperfusion there were no statistically significant differences between the groups for these variables. Steib et al (1997) were also unable to demonstrate differences in plasma lactate concentrations when comparing patients transplanted with these techniques. Many factors contribute to acidosis and hyperlactatemia during liver transplantation such as blood usage, temperature, fluid administration and extrahepatic lactate clearance. The sensitivity of these markers to indicate tissue hypoxia during liver transplantation may therefore be low. It is also possible that the small numbers of patients studied make conclusions subject to type II statistical error. This may explain why this study does not confirm the differences in the degree of acidaemia following reperfusion with the 2 techniques found in the previous chapter which included data from more patients.

An alternative explanation for the differences between the groups is altered oxygen demand. Temperature has a major effect on metabolic rate and hypothermia occurs frequently during liver transplantation. Patients in the venovenous bypass group had lower pulmonary artery blood temperatures during the anhepatic period than those operated on using the piggyback technique and these differences persisted following reperfusion. A change in oxygen consumption of approximately 10% per degree Celsius has been demonstrated during cooling of febrile critically ill patients (Manthous et al 1995). It is therefore likely that differences in temperature between the groups contributed significantly to the differences in  $VO_2$  observed. Identical methods of temperature conservation were employed in both groups. Differences probably resulted from heat loss associated with extracorporeal circulation in the venovenous bypass group, and the shorter duration of the anhepatic period using the piggyback technique with which fewer anastomoses are required. Temperature differences persisted at 90 minutes following reperfusion indicating the importance of temperature conservation during liver transplantation. Hypothermia can have detrimental effects on coagulation, platelet function, cardiac function, and electrolyte

balance in addition to affecting metabolic rate. If differences in body temperature between the techniques persist into the immediate postoperative period, as is likely based on the data in this study, clinically relevant differences in time to recovery of consciousness may occur. These questions require examination in further studies.

If differences in the decrease in  $\text{VO}_2$  during the anhepatic phase were primarily a result of supply limitation a greater oxygen debt might be expected in the venovenous bypass group. The difficulty interpreting acid-base changes in this setting have been discussed above but a greater increase in  $\text{VO}_2$  following reperfusion might have been anticipated in the venovenous bypass group as oxygen debt was paid off. Again, many factors interact at this time but the parallel changes which occurred support the notion that body temperature was an important factor in this study.

The relation between cardiac output, temperature and  $\text{VO}_2$  were confirmed when correlations were examined for pooled data. These correlations confirm the physiological associations between these variables but do not enable conclusions to be drawn regarding the relative importance of cardiac output and temperature in explaining the differences between the groups. The weak correlation between changes in cardiac index and temperature was interesting. These variables correlate during cooling of febrile patients (Manthous et al 1995) which raises the possibility that some of the difference in cardiac output between the groups in the present study occurred as a result of differences in metabolic demand because of temperature differences.

Differences in  $\text{VCO}_2$  between the groups were less marked than for  $\text{VO}_2$  and did not reach statistical significance. This may also represent type II error, but was also not unexpected because  $\text{CO}_2$  stores in the body are large and are influenced by factors other than aerobic metabolism, notably acid-base status.

## CONCLUSIONS

- 1) Cardiac output is greater during the anhepatic period of liver transplantation when the piggyback technique is used compared to venovenous bypass.
- 2)  $\text{VO}_2$  is greater during the anhepatic period with the piggyback technique. This probably occurs because of better oxygen delivery to tissues and differences in oxygen demand as a result of temperature differences.
- 3) Hypothermia appears to be less severe when the piggyback technique is used in comparison with venovenous bypass.

### A COMPARISON BETWEEN REPERFUSION VIA THE PORTAL VEIN AND VIA THE HEPATIC ARTERY DURING LIVER TRANSPLANTATION.

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#### OBJECTIVES

- 1) To compare changes in  $VO_2$  and  $VCO_2$  associated with reperfusion via the portal vein or the hepatic artery.
- 2) To compare the acid-base changes occurring following reperfusion with each technique.
- 3) To compare the cardiovascular changes which occur at reperfusion with each technique.

#### BACKGROUND

Graft reperfusion during liver transplantation is associated with complex physiological changes some of which were investigated in chapter 5. The clinical relevance of these changes can be considered in 2 categories: *immediate* and *delayed*. The immediate effects include alterations in cardiovascular and acid-base status, together with rapid changes in metabolic rate, which may acutely compromise cardiac, vascular and cerebral function. The delayed effects are more subtle and less well described but probably result from the process of *reperfusion injury* to the graft itself. Reperfusion injury is initiated at the time of vascular reperfusion and is characterised by endothelial injury in hepatic sinusoids, a reduction in blood flow these vessels, and hepatocyte damage, all of which result in graft dysfunction in the post operative period (Bzeizi et al 1997). Some degree of reperfusion injury probably occurs in all transplanted livers, but it comprises a spectrum from clinically insignificant to primary non-function requiring re-transplantation. The clinical and economic costs of reperfusion injury are significant particularly if prolonged intensive care or re-transplantation are required (Spanier et al 1995). The aetiology of reperfusion injury is incompletely understood but oxygen derived free radicals have a central role in the initiation and progression of



the process (Bzeizi et al 1997). Improvements in organ retrieval techniques, subsequent preservation, and a reduction in ischaemic times have dramatically improved graft survival but primary graft dysfunction remains a significant clinical problem.

At the time of graft reperfusion itself, the ideal technique would minimise both immediate and delayed complications. The previous chapter compared the piggyback and venovenous bypass techniques focusing on the anhepatic period. Traditionally reperfusion is performed via the portal vein which is frequently a technically easier vessel to anastomose. The portal vein carries a higher flow (typically  $1\text{L}\cdot\text{min}^{-1}$ ) in comparison with the hepatic artery (typical flow  $0.5\text{L}\cdot\text{min}^{-1}$ ) (Ganong 1991). Early re-anastomosis re-establishes normal venous drainage from the gut which may be compromised during the anhepatic period even when venovenous bypass is used. Potential disadvantages of portal vein reperfusion include the rapid large increase in venous return which may compromise cardiac function, and the simultaneous release into the circulation of ischaemic metabolites from both the gut and the graft which could contribute to cardiovascular and cerebral complications at this time (Carton et al 1994). The oxygen content of portal venous blood during health is significantly lower than in arterial blood and following reperfusion may be reduced further from normal levels as a result of haemodilution and oxygen debt in the gut. Reperfusion via the hepatic artery has not traditionally been practised because of lower total flow and uncertainties regarding the adequacy of flow within the graft itself, although the oxygen content and pressure of blood in this vessel are higher. Anatomical anomalies may also make the hepatic artery technically more difficult to anastomose. However, there are potential advantages to this approach which include less cardiovascular disturbance and a staged release of ischaemic metabolites into the systemic circulation.

There are no studies in human liver transplantation which compare in detail reperfusion via the portal vein with primary hepatic arterial reperfusion. This chapter describes a prospective observational study in which these techniques were compared

with respect to changes in oxygen consumption (as a marker of graft oxygen uptake), acid-base changes, and cardiovascular changes in the immediate post-reperfusion period.

## **METHODS**

### **Patients**

20 patients were prospectively studied (10 in each group)(table 7.1). The study was not randomised and the decision regarding which technique was employed was made by the surgeon at the time of operation based on operative findings. In all patients the piggyback technique was employed. The use of temporary portacaval shunting is indicated in table 7.1). The cases in which no shunt was used had a period of portal occlusion at the time of recipient hepatectomy during which no haemodynamic disturbance occurred. Anaesthetic management and cardiovascular monitoring in all cases were identical to that described in the previous chapters.  $VO_2$  and  $VCO_2$  were measured throughout using the Deltatrac metabolic monitor recording data to computer each minute. Calibration and technique of metabolic recordings were as previously described.

### *Management of reperfusion*

*Portal vein group:* In these cases the portacaval shunt was taken down and reperfusion occurred after the portal vein anastomosis was completed. This was followed by hepatic arterial anastomosis.

*Hepatic artery group:* In these cases the portacaval shunt was left in place while the hepatic artery was anastomosed and reperfusion performed. Thereafter the portacaval shunt was taken down and portal vein anastomosis carried out.

Preservation of grafts and flushing prior to reperfusion was identical in both groups. Following reperfusion adrenaline was administered to treat haemodynamic disturbance as clinical indicated.

Table 7.1: Demographic and descriptive data. n = 10 in each group

	Portal vein group	Hepatic artery group
Diagnosis		
Primary Biliary Cirrhosis	4	6
Alcoholic Liver Disease	2	1
Cryptogenic Cirrhosis	0	2
Chronic Active Hepatitis	0	1
Subacute Hepatic Failure	2	0
Chronic Rejection of Transplant	1	0
Primary Sclerosing Cholangitis	1	0
Age (mean (range))	51 (35-60)	45 (24-65)
Sex (F/M)	6/4	8/2
Use of portocaval shunt (n/10)	6/10	8/10

### Measurements

#### *VO<sub>2</sub> and VCO<sub>2</sub>*

The following time periods were chosen for analysis:

Time period I (pre-reperfusion): The mean of the 10 minute period immediately prior to reperfusion.

Time period II: The mean of the 10 minute period from 10-20 minutes following reperfusion of the graft.

Time period III: The mean of the 10 minute period from 10-20 minutes following reanastomosis of the second vessel.

Time period IV: The mean of the 10 minute period starting 90 minutes following reperfusion.

#### *Cardiovascular parameters:*

As discussed in chapter 5 cardiac output measurements are unreliable in the immediate post-reperfusion period. Cardiac output was therefore compared immediately prior to reperfusion (during time period I) and following anastomosis of the second vessel (time period III). Mean arterial pressure was compared 10 minutes before and 10 minutes after reperfusion, and 10 minutes before and after reanastomosis of the second vessel.

#### *Acid-base variables and temperature:*

The evolution of acid-base changes following reperfusion were examined by measuring plasma whole blood lactate, hydrogen ion, and standard bicarbonate concentrations and  $\text{PaCO}_2$  at the following time points:

Time point A: prior to reperfusion.

Time point B: 30 minutes following reperfusion.

Time point C: 60 minutes following reperfusion.

Pulmonary artery blood temperature was compared immediately before and 1 hour after reperfusion.

#### *Post-reperfusion injury*

As an index of post-reperfusion injury the plasma alanine aminotransferase (ALT) concentrations were compared 24 hours after transplantation.

#### *Statistical analysis.*

Changes in physiological variables between the periods of interest were compared between the groups. Data were not normally distributed. The Mann-Whitney U test with Bonferroni's correction for multiple comparisons was used for analysis.

## RESULTS

19 patients survived transplantation with good graft function and were alive 3 months following surgery. One patient in the hepatic artery group developed a portal vein thrombosis requiring surgical intervention on day 4 post transplantation, and subsequently an hepatic artery thrombosis on day 5 post transplantation. This was complicated by graft failure, and the patient died prior to a further liver becoming available.

The groups were similar for all physiological variables prior to reperfusion (table 7.2). Changes in  $\text{VO}_2$  for each patient over the 4 time periods are illustrated in figures 7.1 and 7.2. In the portal vein group a single large increase in  $\text{VO}_2$  occurred following reperfusion, with little further change occurring after anastomosing the hepatic artery. In the hepatic artery group the increase in  $\text{VO}_2$  was biphasic with a significant further increase in  $\text{VO}_2$  occurring when the portal vein was anastomosed. These differences between the groups were statistically significant (figure 7.2). The overall increase in  $\text{VO}_2$  between time periods I and IV was similar for both groups. Typical plots of continuous data for a patient in each group are shown in figure 7.3. Changes in blood temperature over the period of interest were also similar for both groups (Table 7.3).

Changes in  $\text{VCO}_2$  for each group between the time periods were not significantly different between the groups except between time periods III and IV when the increase was statistically greater in the hepatic artery group, although the magnitude of this difference was small (figure 7.4).

Cardiovascular changes are shown in tables 7.4 and 7.5. Within both groups a small decrease in mean arterial pressure accompanied reperfusion but differences between the groups were not significant. No change in mean arterial pressure occurred when the second vessel was opened. Cardiac index increased over the study period in both groups; there was no difference in the magnitude of these changes between the groups. However, adrenaline usage over the reperfusion period was significantly greater in the portal vein group ( $P=0.014$ )(figure 7.5).

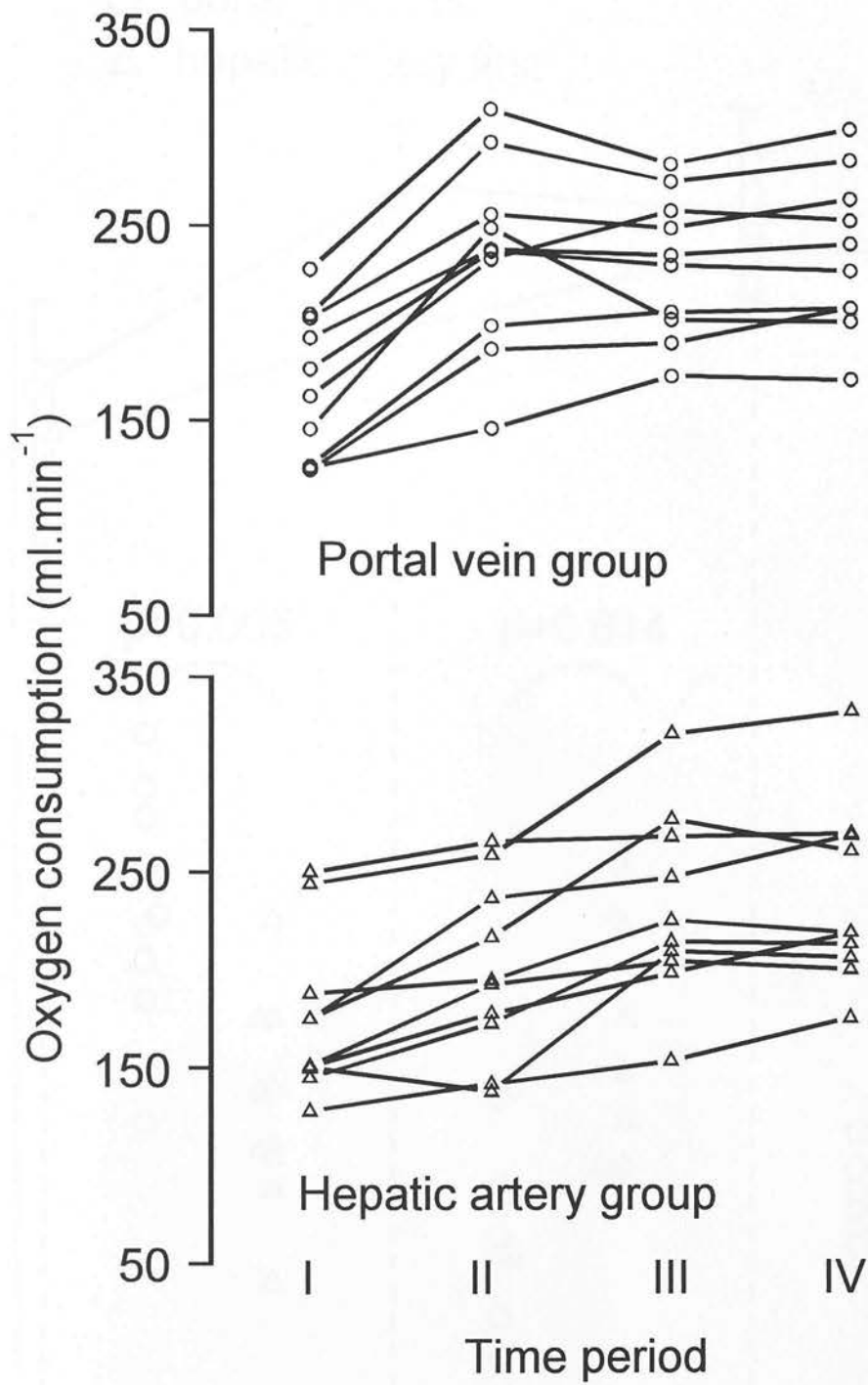


Figure 7.1:  $VO_2$  data for individual patients.



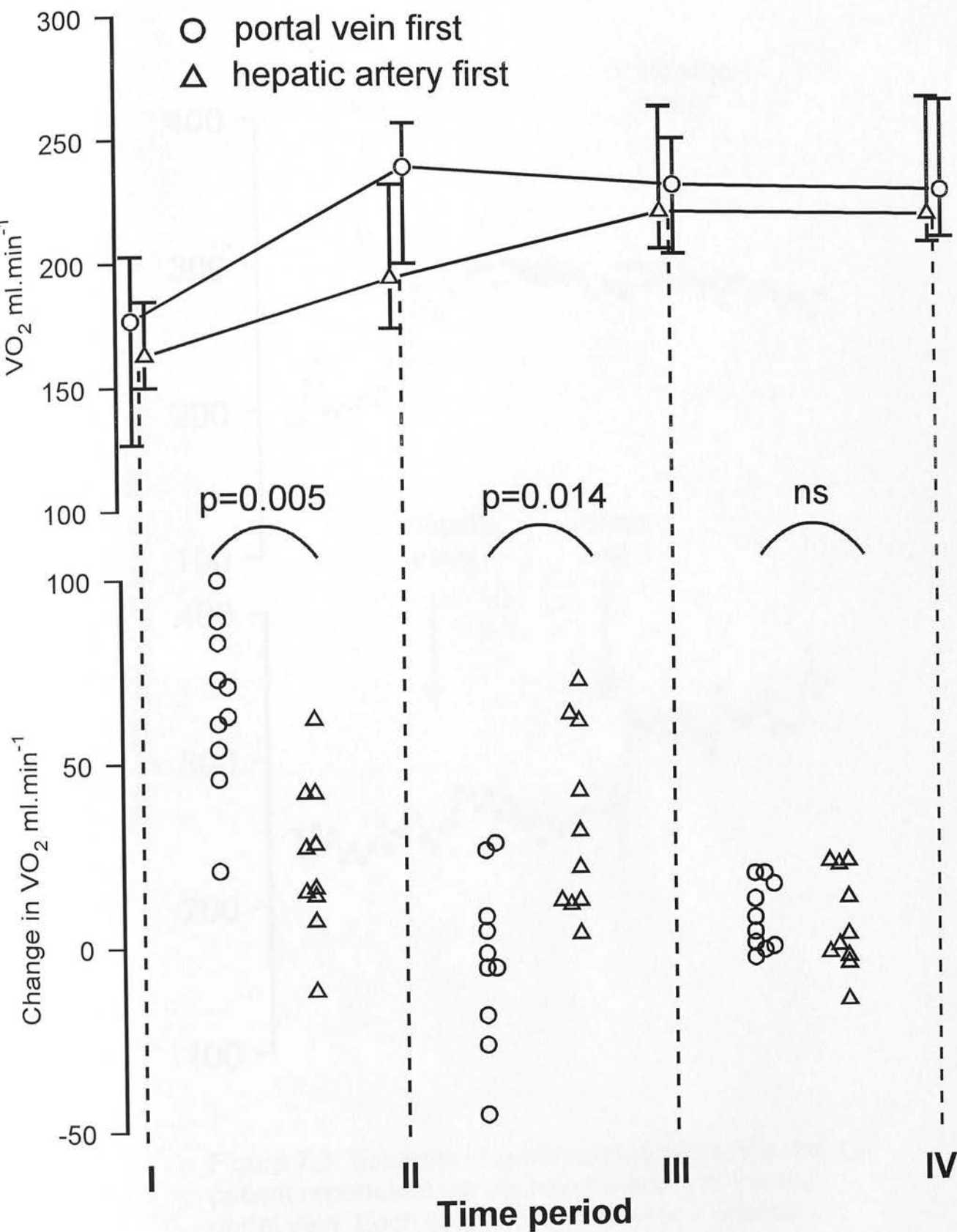


Figure 7.2: Changes in oxygen consumption ( $VO_2$ ) after reperfusion with the portal vein or hepatic artery first.  $n = 10$  in each group. *Upper panel* shows medians (1st, 3rd quartiles). *Lower panel* shows changes for individual patients between time periods.

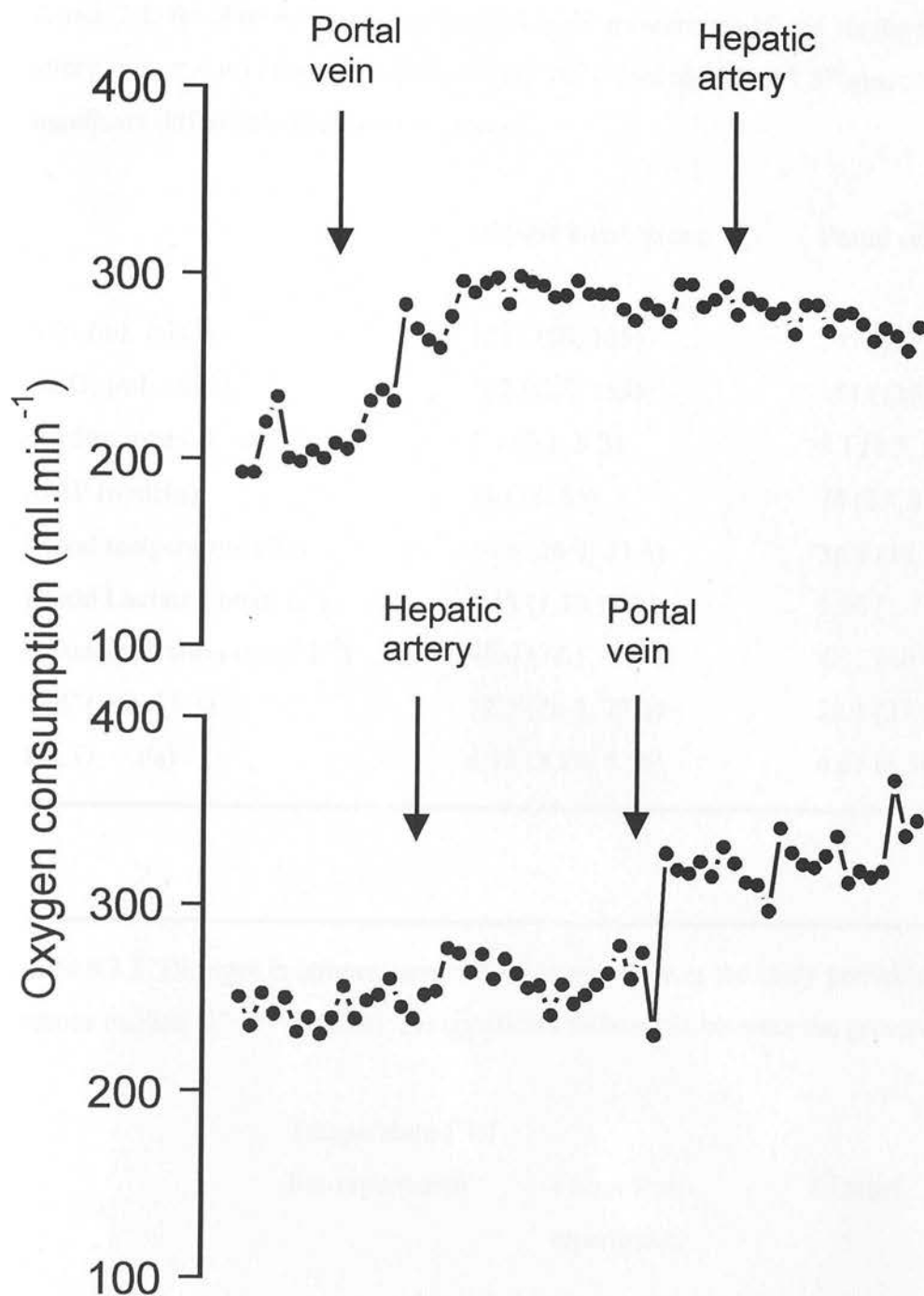


Figure 7.3: Example of continuous data for  $VO_2$  from a patient reperfused via the hepatic artery or via the portal vein. Each data point represents 1 minute.

TABLE 7.2: Baseline data prior to reperfusion for patients reperfused via the hepatic artery or portal vein (n = 10 in each group). All values median (1<sup>st</sup>, 3<sup>rd</sup> quartile). No significant differences between the groups.

	Hepatic artery group	Portal vein group
VO <sub>2</sub> (mL.min <sup>-1</sup> )	163 (150, 185)	177 (127, 203)
VCO <sub>2</sub> (mL.min <sup>-1</sup> )	132 (128, 159)	151 (135, 157)
Cardiac index (L.min <sup>-1</sup> .m <sup>-2</sup> )	5.4 (5.1, 8.2)	5.1 (4.7, 6.7)
MAP (mmHg)	78 (73, 85)	74 (63, 85)
Blood temperature (°C)	36.6 (36.3, 37.4)	36.7 (36.4, 37.2)
Blood Lactate (mmol.L <sup>-1</sup> )	1.55 (1.35,1.82)	1.90 (1.75, 2.09)
H <sup>+</sup> concentration (nmol.L <sup>-1</sup> )	40.0 (37.1, 44.4)	42.1 (40.9, 47.0)
SBC (mmol.L <sup>-1</sup> )	22.3 (20.5, 23.3)	22.1 (21.0, 23.6)
PaCO <sub>2</sub> (kPa)	4.12 (3.88, 4.56)	4.67 (4.36, 4.96)

TABLE 7.3: Changes in temperature within the groups over the study period. All values median (1<sup>st</sup>, 3<sup>rd</sup> quartile). No significant differences between the groups.

	Temperature (°C)		
	Pre-reperfusion	1 hour Post-reperfusion	Change
Hepatic artery	36.6 (36.3, 37.4)	37.0 (36.8, 37.7)	0.4 (0.3, 0.5)
Portal vein	36.7 (36.4, 37.2)	37.1 (36.8, 37.4)	0.4 (0.3, 0.7)

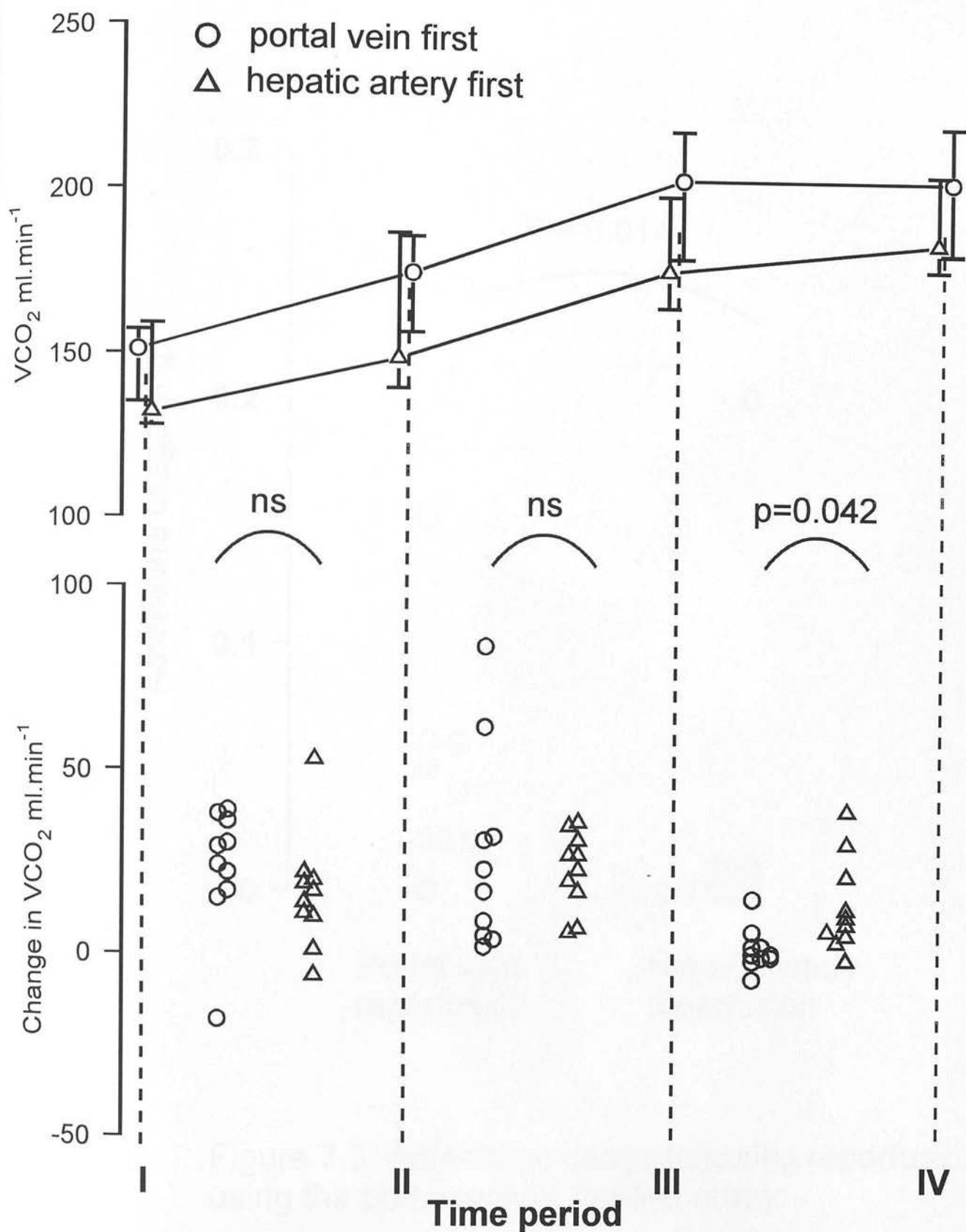


Figure 7.4: Changes in carbon dioxide elimination ( $VCO_2$ ) after reperfusion with the portal vein or hepatic artery first. *Upper panel* shows median (1st, 3rd quartiles)  $VCO_2$  for each time period. *Lower panel* shows changes for individual patients between time periods.

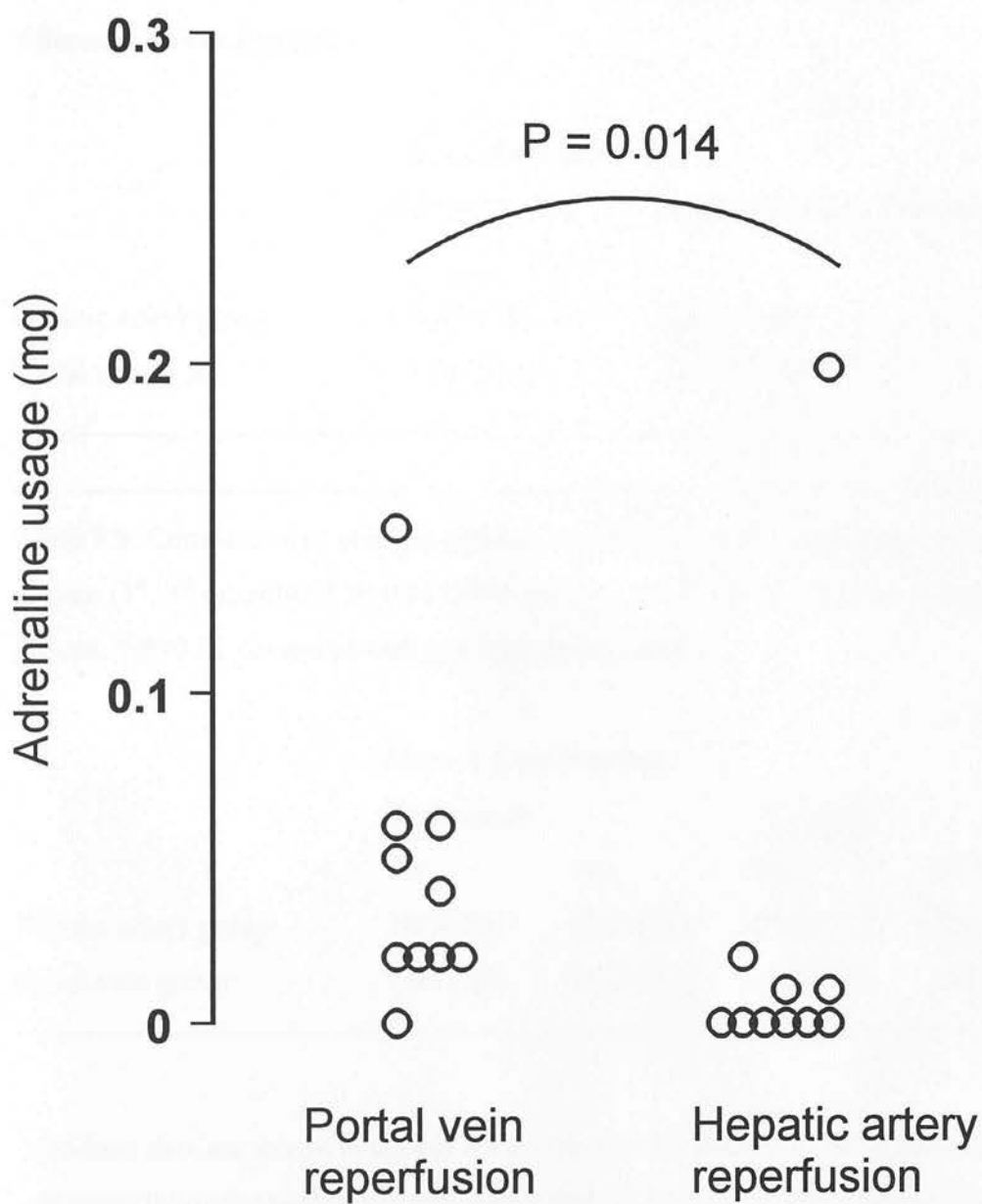


Figure 7.5: Adrenaline usage following reperfusion using the portal vein or hepatic artery.

Table 7.4: Comparison of changes in cardiac index between the groups. All values median (1<sup>st</sup>, 3<sup>rd</sup> quartile). \* P<0.01 for changes *within* groups. No significant difference *between* groups.

	Cardiac index (L.min <sup>-1</sup> .m <sup>-2</sup> )	
	Pre-reperfusion	Post-reperfusion (both vessels)
Hepatic artery group	5.4(5.1,8.2)	6.4(5.4,8.6)*
Portal vein group	5.1 (4.7,6.7)	6.8(6.1,7.4)*

Table 7.5: Comparison of changes in mean arterial pressure for the groups. All values median (1<sup>st</sup>, 3<sup>rd</sup> quartile). \* P<0.01 *within* groups. No significant differences *between* groups. \* P<0.01 compared with pre-reperfusion values.

	Mean Arterial Pressure			
	Reperfusion		2 <sup>nd</sup> vessel	
	Pre	Post	Pre	Post
Hepatic artery group	78(73,85)	67(58,70)*	68(61,77)	72(62,76)
Portal vein group	74(63,85)	64(57,70)*	66(60,68)	68(61,71)

Acid-base data are shown in figures 7.6 to 7.9. These indicate a trend towards greater acidaemia following portal vein reperfusion than in the hepatic artery group. Changes in blood lactate concentration and standard bicarbonate concentration were similar between the groups. The rate of increase in PaCO<sub>2</sub> was slower in the hepatic artery group.

The time between reperfusion and and opening of the second vessel was significantly longer in the portal vein group than in the hepatic artery group (median (1<sup>st</sup>, 3<sup>rd</sup>



quartile): 52 (45, 69) vs 25 (20, 36),  $P<0.01$ ). There was no significant difference between plasma ALT concentrations 24 hours post transplantation between the groups (fig 7.10).



Figure 7.10: Changes in plasma ALT concentrations (IU/L) over 24 hours post-transplantation for two groups. The top line (solid circles) represents the higher group, and the bottom line (open circles) represents the lower group. Error bars are shown for each data point.

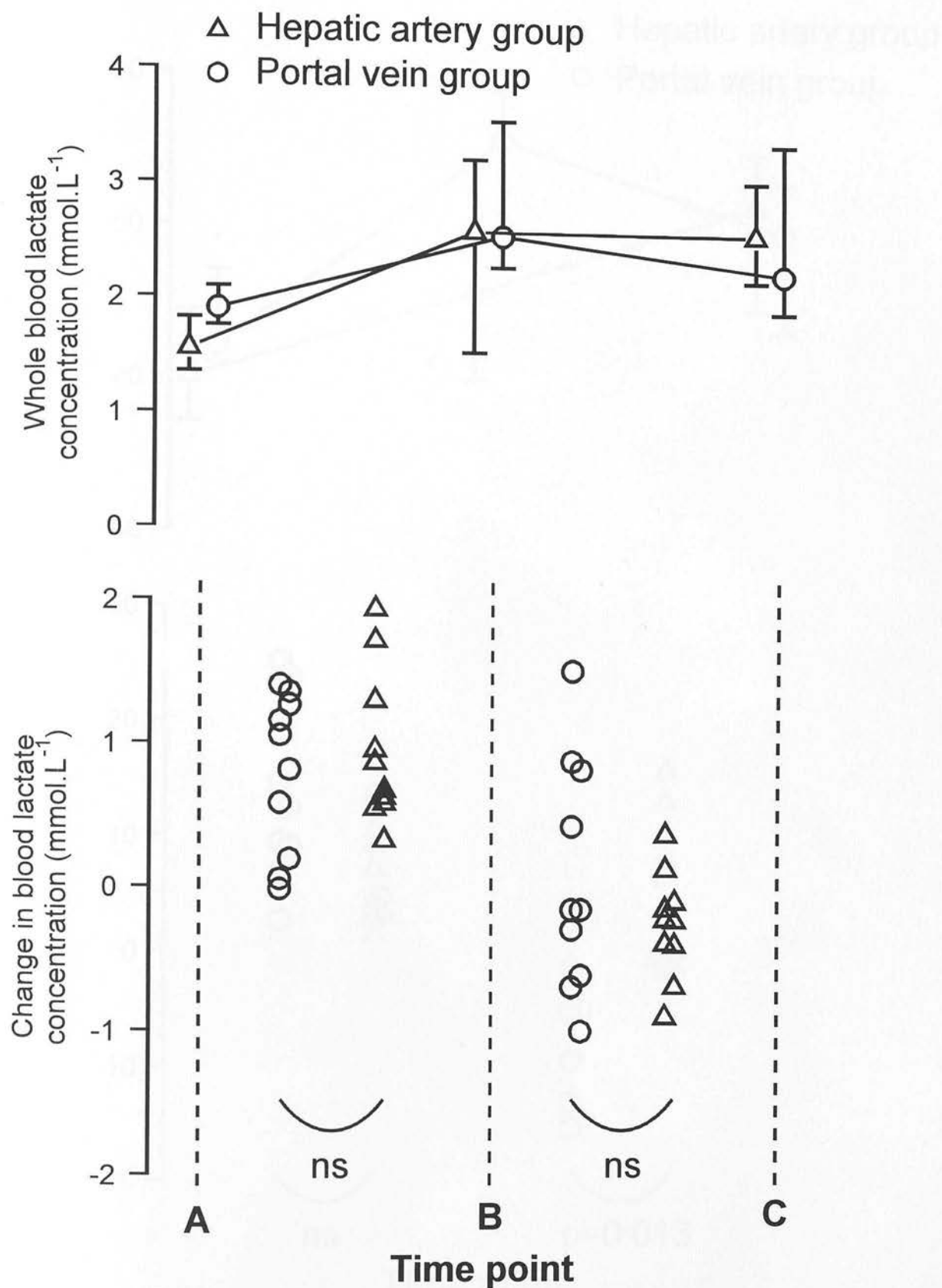


Figure 7.6: Changes in blood lactate concentration following reperfusion. *Upper panel* shows median (1st, 3rd quartile) lactate concentration at each time point. *Lower panel* compares changes between each time point for the 2 groups.

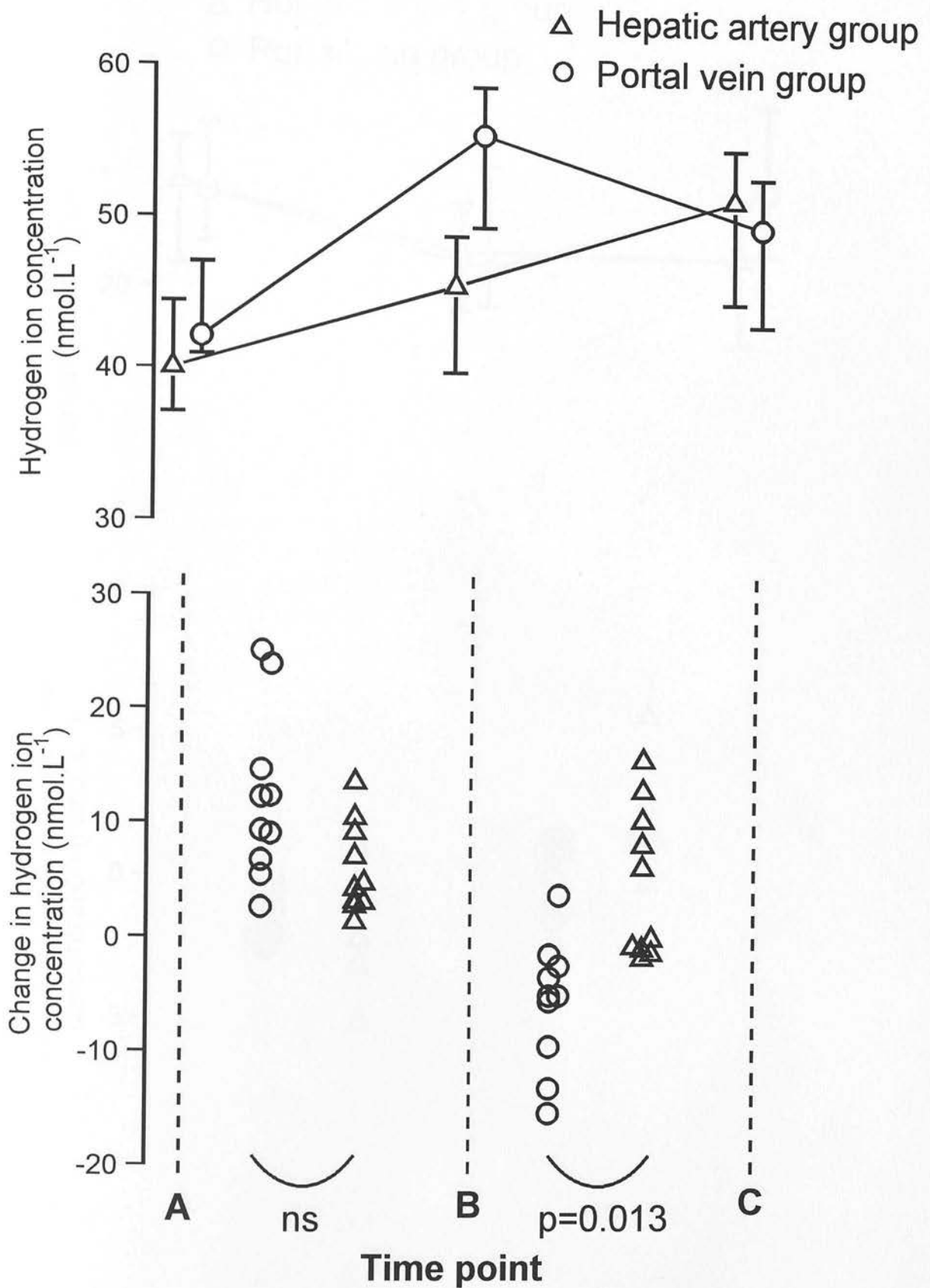


Figure 7.7: Changes in hydrogen ion concentration following reperfusion. *Upper panel* shows median (1st, 3rd quartile) hydrogen ion concentration at each time point. *Lower panel* compares changes between each time point for the 2 groups.

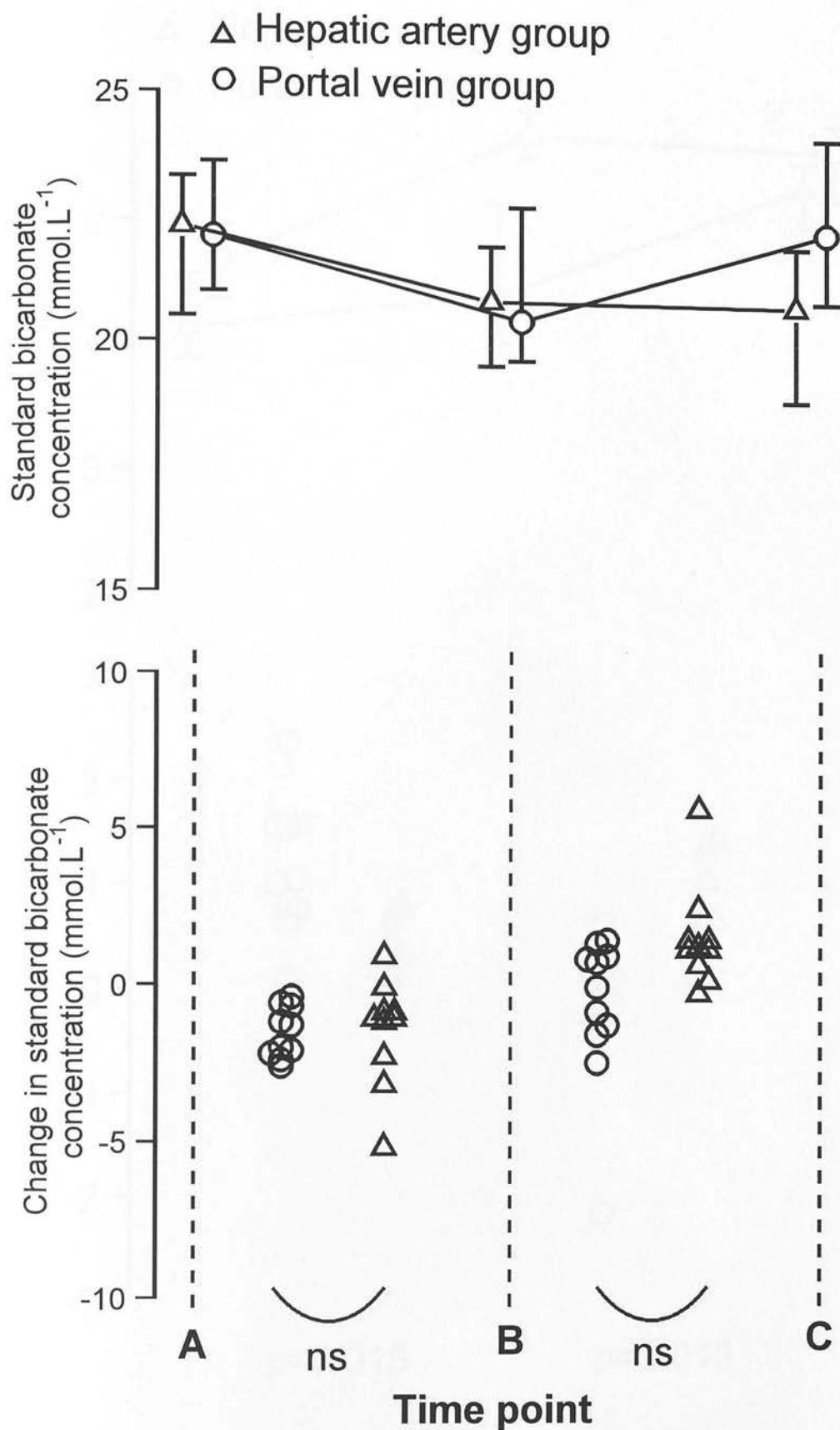


Figure 7.8: Changes in standard bicarbonate concentration following reperfusion. *Upper panel* shows median (1st, 3rd quartile) standard bicarbonate concentration at each time point. *Lower panel* compares changes between each time point for the 2 groups.

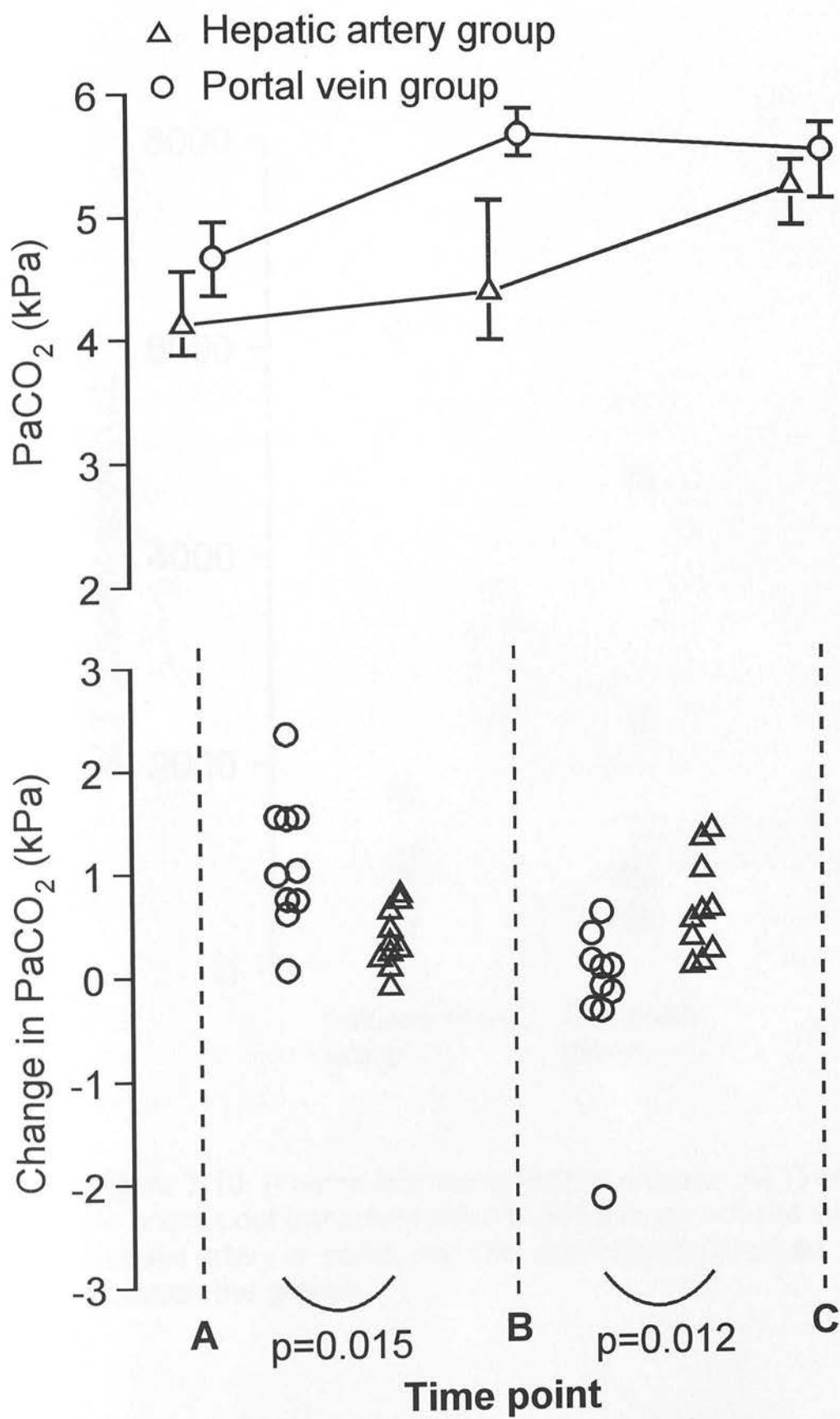


Figure : Changes in PaCO<sub>2</sub> following reperfusion. *Upper panel* shows median (1st, 3rd quartile) PaCO<sub>2</sub> at each time point. *Lower panel* compares changes between each time point for the 2 groups.

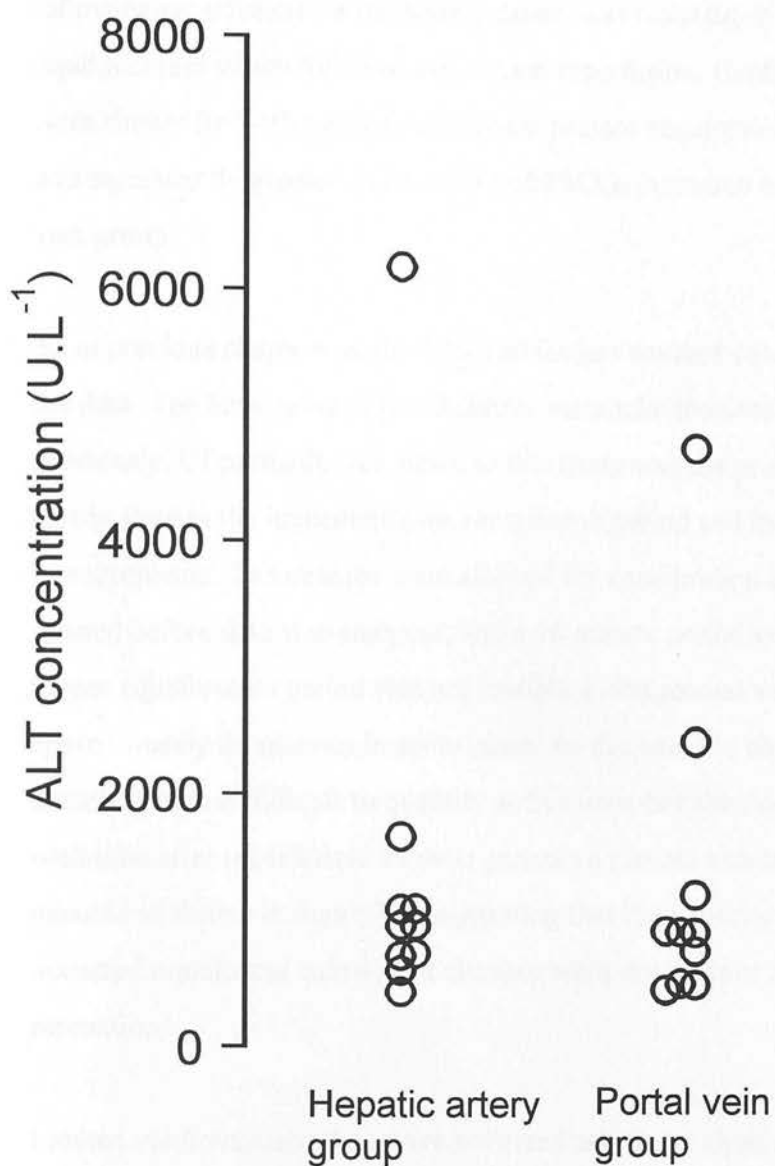


Figure 7.10: Plasma Alanine aminotransferase (ALT) concentrations 24 hours post transplantration in patients reperfused via the hepatic artery or portal vein. No significant differences between the groups.



## DISCUSSION

The principal findings of this study were that the increase in  $\text{VO}_2$  which occurred following reperfusion via the hepatic artery was biphasic, in contrast to the single rapid increase which followed portal vein reperfusion. Cardiovascular parameters were similar for both groups but the vasopressor requirement in the portal vein group was significantly greater. Acidaemia and  $\text{PaCO}_2$  increased more rapidly in the portal vein group.

As in previous chapters methodological factors warrant consideration in interpreting the data. The limitations of the Deltatrac metabolic monitor have been discussed previously. Of particular relevance to this study was the problem of physiological steady state in the immediate post reperfusion period and its effect on the accuracy of measurements. Ten minutes were allowed for equilibration after each vessel was opened before data was analysed, and a 10 minute period was then averaged. A longer equilibration period was not feasible as the second vessel was opened after approximately 20 minutes in some cases. As discussed in chapter 5 inaccuracy from unsteady state is difficult to quantify at this time, but should decrease exponentially with time after reperfusion. In most patients a plateau was reached within a few minutes as shown in figure 7.3, suggesting that the majority of re-equilibration occurred rapidly and subsequent changes were not a major source of error for  $\text{VO}_2$  estimation.

Limited cardiovascular data were collected and the analysis of derived haemodynamic variables was avoided. Measurement of cardiac output with the continuous thermodilution method used is inaccurate in the post-reperfusion period because of rapid changes in temperature, infusion of fluids, and cardiovascular instability (Bottiger et al 1997). Comparison between values from the pre-reperfusion and 1 hour post-reperfusion periods were considered useful and indicated no differences between the groups. It has already been shown that relatively minor changes in cardiac output occur after reperfusion when the piggyback technique is used, so it was not surprising that differences between the groups in this study were not

significant.

The most clinically relevant cardiovascular complication of reperfusion during liver transplantation is systemic hypotension which occurs primarily because of vasodilatation (Carton et al 1994). Controversy exists regarding the importance of myocardial dysfunction at this time, in part because most studies have based conclusions on calculated variables such as stroke work and stroke volume. For these variables to accurately reflect myocardial function preload and afterload conditions must remain constant which is not the case during the reperfusion period. Most studies indicate that myocardial dysfunction is not usually severe following reperfusion (Carton et al 1994). The most frequent complication is arrhythmia which results from acute electrolyte and acid-base disturbance and reduced coronary perfusion from systemic hypotension and elevated cardiac filling pressures. No difference was found in mean arterial pressure between the groups in the present study, but the requirement for vasopressors was significantly greater in the portal vein group. These data are consistent with less vasodilatation, and possibly myocardial dysfunction, in the hepatic artery group but further specific studies are required to confirm this hypothesis.

This study was observational, was not randomised and the choice of technique was made by the surgeon. In addition, the time required for anastomosis of the second vessel was significantly longer in the portal vein group. These are all potential sources of bias which may have influenced the results obtained, and require consideration if a larger outcome study is planned.

The primary objective of the study was to compare changes in  $\text{VO}_2$  between the groups and clear differences were found. Several factors may contribute to the changes in  $\text{VO}_2$  which occur following reperfusion. Oxygen uptake by the graft probably accounts for most of the increase observed and previous studies have related the magnitude of this change to graft function (Svensson et al 1989, Steltzer et al 1992, Gubernatis et al 1989). Oxygen debt incurred in other tissues during the

anhepatic period, particularly the gut, is also relevant as suggested in the previous chapter. It is unknown if tissue oxygen extraction either in the graft or in other organs is impaired in the post reperfusion period, but if present this may result in regional oxygen supply dependency which is not apparent from global measures such as  $\text{VO}_2$ . The importance of temperature has also been discussed in the previous chapters, as was the possible contribution of oxygen derived free radicals. Endotoxaemia occurs during liver transplantation (Miyata et al 1989, Welte et al 1996) which could alter  $\text{VO}_2$  by stimulating the systemic inflammatory response syndrome (Oudemans-van Straaten et al 1996). Furthermore, adrenaline may alter  $\text{VO}_2$  as was discussed in the introduction to this thesis. The relative contribution of these various factors make interpretation of the data in a human study performed under clinical conditions difficult. A previous study attempted to quantify oxygen uptake across the transplanted liver by measuring flow and oxygen content in hepatic arterial, portal venous, and hepatic venous blood but the measurement errors associated with this method are so large that the validity of the data is questionable (Russell et al 1995).

In the present study the piggyback technique was used in all cases making the groups comparable in this respect. Temperature changes over the reperfusion period were also similar. Leaving aside the contribution of hypothetical factors such as endotoxaemia and free radical formation there are 2 likely explanations for the differences between the groups:

*Differences in hepatic oxygen uptake:* It is possible that oxygen uptake by the graft was slower in the hepatic artery group, most likely as a result of less efficient oxygen supply. If correct, this observation is important because it suggests warm ischaemia of the graft is prolonged which could increase ischaemic injury and adversely affect subsequent function. The portal venous system is a high-flow, low pressure, low resistance circulation which drains directly into the hepatic sinusoids from which oxygen diffuses to hepatocytes. In contrast, the hepatic arterial system is a complex high pressure system with high resistance in the hepatic arterioles. Blood reaches the sinusoids via a variety of routes each associated with a drop in pressure from arterial

to sinusoidal levels (Williams and Warwick 1980). The chief pathway is via a system of capillaries which form a plexus around the interlobular hepatic ductules and drain into various branches of the portal veins, venules, and hepatic sinusoids. This system is rich in capillary sphincters such that, in health, blood flow is dynamically altered according to regional requirements within the liver. The function of this system in reperfused livers following cold preservation is unknown. Only a small proportion of hepatic arterial blood directly enters the sinusoids (Williams and Warwick 1980). Hepatocytes distant to the portal triads exist under conditions of relative hypoxia, and oxygen consumption by these cells is likely to be limited by supply. Abnormal blood flow within the graft is common following reperfusion (Bzeizi et al 1997) so that differences between hepatic arterial and portal venous reperfusion could be clinically relevant. The overall changes in  $\text{VO}_2$  over the study period were similar between the groups but this is unlikely to be a sufficiently sensitive marker of later graft function. Similarly, there was no difference between the groups in the 24 hour ALT values, a useful marker of reperfusion injury, but a larger study is needed to specifically address this question. In future work tests of graft function such as indocyanine green clearance production may be valuable as a more sensitive and specific marker of early graft function (Jalan et al 1994).

*Differences in oxygen debt:* An alternative explanation for the differences observed relates to the rate at which oxygen debt incurred during the anhepatic period is paid off. The best clinical indices of oxygen debt are acid-base balance. Considering all acid-base parameters together the overall pattern observed suggested that in the portal vein group reperfusion was associated with a sudden release of acid from the graft and other tissues such as the gut. By the time the hepatic artery was perfused the oxygen debt had been cleared and little further change occurred. Conversely, in the hepatic artery group a lesser degree of acidaemia occurred following reperfusion but a further acid load followed portal vein anastomosis. The second load may originate from the gut or from the graft itself. Assuming ischaemic metabolites contribute to physiological instability following reperfusion this decrease in the rate of release may be beneficial at least in high risk patients. A clear relationship between altered cerebral

blood flow velocity and tourniquet release has been demonstrated in humans undergoing limb surgery, and closely linked to the release of ischaemic metabolites particularly changes in  $\text{PaCO}_2$  (Hirst et al 1990). This may be of particular relevance to the post reperfusion liver transplant patient. Increases in cerebral blood flow and cerebral blood flow velocity have been clearly demonstrated following reperfusion in patients undergoing elective liver transplantation and may persist for several hours (Doblar et al 1995, Skak et al 1997, Philips et al 1998). The factors which mediate this phenomenon are unresolved but hyperventilation prior to reperfusion has been shown to attenuate the increase in cerebral blood flow velocity which occurs (Doblar et al 1995). The rate of rise of  $\text{PaCO}_2$  was slower in the hepatic artery group and it is a reasonable hypothesis that this might be associated with less cerebrovascular disturbance.

The relation between different acid-base variables following reperfusion merits further consideration in the light of the findings of this study, particularly as the changes in standard bicarbonate concentration were unremarkable. The increase in  $\text{PaCO}_2$  following reperfusion is attributable to several factors which were discussed in chapter 5. The primary determinant of  $\text{VCO}_2$  is alveolar ventilation. Minute ventilation remained constant over the study period although it was shown in chapter 5 that a small increase in alveolar ventilation occurs in association with increased pulmonary perfusion following reperfusion. The increase in  $\text{PaCO}_2$  thus results from increased metabolic production. This occurs in part from buffering of the released acid load, which should be associated with a decrease in standard bicarbonate concentration. In addition, carbon dioxide originates from increased aerobic metabolism by tissues. Carbon dioxide produced by oxidative phosphorylation is transported in the blood in three forms: dissolved, as carbamino compounds (primarily bound to haemoglobin), and as bicarbonate (Nunn 1977). Of these bicarbonate is quantitatively most important. Bicarbonate is generated in red blood cells from  $\text{CO}_2$  by carbonic anhydrase and then effluxes into the plasma in exchange for chloride ions (the Hamburger effect). Hydrogen ions produced in this reaction are buffered by reduced haemoglobin within the red cells themselves. Reperfusion during liver transplantation



is associated with a rapid decrease in mixed venous haemoglobin oxygen saturation so that the buffering capacity of haemoglobin at this time is large (Riano et al 1991). Thus increased production of carbon dioxide within tissues, as metabolic rate increases, is associated with significant bicarbonate generation. This may explain why the release of an acid load at reperfusion is not accompanied in all cases by acidosis. High capacity for red cells to carry carbon dioxide and convert it to bicarbonate is also the likely explanation for the less marked differences between the two groups in  $VCO_2$  in comparison with  $VO_2$  following reperfusion.

## CONCLUSIONS

- 1) Reperfusion of the donor liver via the hepatic artery rather than the portal vein was associated with a slower increase in  $VO_2$ .
- 2) The release of acid load following reperfusion occurred more gradually when the hepatic artery was used in comparison with the portal vein.
- 3) Adrenaline requirement was less when the hepatic artery was used suggesting greater cardiovascular stability.
- 4) No differences in early graft function were apparent from this observational study but this requires confirmation in future work.



### GENERAL DISCUSSION

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This thesis has centred on oxygen kinetics in patients with liver disease. In patients with fulminant hepatic failure oxygen transport and uptake were examined with particular reference to the effect of N-acetylcysteine, and energy expenditure was assessed in comparison with truly anhepatic patients during liver transplantation and healthy control subjects. During liver transplantation the changes in gas exchange which occur after graft reperfusion were documented in detail, and two surgical techniques for managing the anhepatic period and for reperfusing the donor graft were compared with reference to oxygen balance. In reviewing previous studies of oxygen kinetics in the critically ill it was clear that, despite the large number of studies which exist, conclusions are contradictory and consensus regarding the importance of oxygen balance in the critically ill is lacking. It is my belief that much of this confusion is attributable to the methodology used in previous work. A primary objective of this thesis was to examine the best available means of investigating oxygen kinetics in patients with liver disease so that potentially confounding factors in the data obtained were recognised.

In chapter 3 two important types of measurement error were examined: the *reproducibility* of oxygen consumption measurements and the effect of *mathematical coupling* on the relationship between oxygen delivery and consumption. Gas exchange measurements of oxygen consumption, made using an automated metabolic monitor, were compared with calculations by the reverse Fick method. This study was performed under the clinical conditions present in most patients examined in subsequent studies, that is a cardiovascular pattern characterised by high cardiac output and small arteriovenous oxygen content difference, and no significant lung injury or requirement for high inspired oxygen fractions. The agreement between these methods of measurement was very poor, and two important observations were

made. First, the relative reproducibility of the Fick method was much worse than the gas exchange method suggesting most of the measurement error occurred from Fick calculations. Second, the Fick method gave values consistently less than gas exchange measurements. I have considered in detail the errors associated with each method of measurement and related these to the conditions present in the patients studied. Although the Fick method for determining oxygen consumption is theoretically correct it assumes complete accuracy of all physiological measurements. The problem with the Fick method is propagation of error. The simple mathematical model derived in chapter 3 to examine the magnitude of errors in the final calculation of oxygen consumption clearly illustrates that when the cardiac output is large and the arteriovenous oxygen content is small the reproducibility of data with the Fick method is likely to be poor even if primary physiological measurements are of acceptable accuracy. In the patients examined in this thesis, therefore, gas exchange measurements were considered most accurate. This may not be the case in other patient groups. For example, in a patient with acute lung injury, high inspired oxygen fractions, high airway pressures, and low mixed venous oxygen saturation the Fick method may perform better.

The bias between the methods of measurement is a consistent finding in studies which compare the methods and may be due, in part, to pulmonary oxygen consumption. Some studies have used this hypothesis to estimate pulmonary oxygen consumption in experimental animals and critically ill humans and at the present time there is no other way of investigating this in vivo (Light 1988, Jolliet et al 1996). Pulmonary oxygen consumption calculated in this way is a highly derived variable which will inevitably be associated with significant inaccuracy. Studies in this area are interesting and potentially valuable, but errors require careful consideration when interpreting data. Work published to date on this subject has not included any assessment of reproducibility.

The importance of mathematical coupling has been central to interpreting the oxygen kinetics literature and was examined in chapter 3. In recent years a consensus has

emerged that mathematical coupling does explain much of the dependence of oxygen consumption on delivery in the critically ill, although agreement is far from universal (Schumacker 1998). Although studies have clearly shown that mathematical coupling *can* explain oxygen supply dependency few studies have clarified *under what circumstances* this is most likely to happen. This is important because gas exchange methods are unavailable in most intensive care units and, as noted above, there are circumstances in which they are insufficiently accurate. In considering this question it was concluded that several factors favour coupling error when interpreting oxygen kinetics data. These are summarised in table 8.1.

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TABLE 8.1: factors which increase the chance of mathematical coupling error in oxygen kinetics studies.

- Large measurement errors in the primary variables
  - Small arterial-venous oxygen content difference which magnifies error by propagation
  - Plotting too few data over too small a range of  $\text{DO}_2$
  - Pooling data from many patients during analysis rather than analysing changes in individuals
  - Study designs which favour positive or negative measurement errors
- 

I believe these factors apply to many published oxygen kinetics studies in the critically ill. A retrospective review supports this conjecture in that studies which used gas exchange methods or made many Fick calculations over a wide range of oxygen delivery have generally failed to demonstrate oxygen supply-dependency whereas those which apparently confirm it made a small number of Fick calculations in conjunction with modest changes in oxygen delivery, often pooling data prior to statistical analysis (Russell and Phang 1994).

This consideration of measurement errors was designed around the study which re-evaluated the effect of N-acetylcysteine on oxygen kinetics in patients with fulminant hepatic failure. The results of an earlier influential study in this area were potentially subject to the errors described above and this was confirmed by the results of my study which found no evidence of improved global oxygen consumption in patients with fulminant hepatic failure during N-acetylcysteine infusion. The cardiovascular effects were also less marked than previously reported and although the number of patients studied was small these observations were more in keeping with findings in other groups of critically ill patients. Pharmacokinetic factors may well explain the immediate yet transient effects observed in some of the patients in this and other studies, and there is a clear need for studies to define the optimum dose and regimen for N-acetylcysteine in critically ill patients.

Although the study in this thesis indicates N-acetylcysteine is unlikely to significantly alter global oxygen transport and uptake in patients with fulminant hepatic failure, the observed effect on outcome in this patient group remains unexplained. This benefit has only been demonstrated by one research group and, although widely accepted, it is possible that the finding is erroneous. Alternatively, it is possible that N-acetylcysteine has alternative mechanisms of action in the critically ill. The drug could alter regional blood flow. A study in critically ill patients with hepatic dysfunction demonstrated improved indocyanine green (ICG) clearance, indicative of either improved hepatic blood flow or ICG extraction, following N-acetylcysteine (Devlin et al 1997), and in a study in septic patients gastric tonometry suggested a modest reduction in gastric mucosal acidosis in those patients in whom cardiac output increased following administration of the drug although no improvement was observed in patients in whom global haemodynamic measurements were unchanged (Spies et al 1994). In patients with sepsis syndrome, N-acetylcysteine attenuated the decrease in gastric intramucosal pH and OER which occurred during transient hyperoxia in comparison with control patients (Reinhart et al, 1995). These effects may be mediated via a vasodilatory effect on microvascular blood flow. Patients with fulminant hepatic failure have elevated plasma concentrations of cyclic guanosine monophosphate (cGMP) (Schneider et al 1994, Harrison et al 1996), and nitrite (Wendon et al 1994) which are indirect markers of nitric oxide activation. N-

acetylcysteine infusion further increases plasma cGMP concentrations in patients with fulminant hepatic failure which may indicate enhanced nitric oxide synthesis (Harrison et al 1996). A similar mechanism, probably mediated via the sulphhydryl group on the molecule, may explain the ability of N-acetylcysteine to reverse tolerance to the vasodilator actions of organic nitrates (Horowitz et al 1988, Boesgaard et al 1992). Although there is little work documenting in detail the haemodynamic effects of N-acetylcysteine in healthy humans, it appears from studies in patients who have recovered from fulminant hepatic failure that the vasodilatory action of the drug is either absent or much less marked in normal individuals (Harrison et al 1991, 1996).

If the hypothesis that N-acetylcysteine beneficially alters microvascular blood flow within tissues is correct, this might improve regional tissue oxygenation even if global measures of oxygen consumption and extraction remain unchanged. A mismatch between oxygen demand and supply within tissues is hypothesised during sepsis (Walley 1996), and is supported by animal models (Humer et al 1996). Similar derangements may also be present in patients with fulminant hepatic failure, in whom control of vascular tone is clearly abnormal.

Animal models indicate that pre-treatment with N-acetylcysteine may be protective in experimental endotoxaemia (Zhang et al 1994, Peristeris et al 1992) and ARDS (Bernard et al 1984, Bernard 1991, Modig and Sandin 1987) if given before the experimental insult. Post-insult treatment with N-acetylcysteine decreased oxidant stress, pulmonary neutrophil influx and lung leak in a rat model of lung injury (Leff et al 1993). It is hypothesised that these actions might be mediated via replenishment of antioxidant defences either through enhanced glutathione synthesis or via a direct antioxidant mechanism. Oxidant defences are depleted in critically ill patients, notably those with sepsis (Goode and Webster 1993, Goode et al 1995) and ARDS (Gadek and Pacht 1996). Depletion of antioxidant defences has also been associated with the development of multiple organ failure and death in the critically ill (Borrelli et al 1996, Cowley et al 1996). These studies suggest a potential therapeutic benefit via restoration of antioxidant defences. Human studies have demonstrated replenishment by N-acetylcysteine of plasma cysteine concentrations and red blood cell and granulocyte glutathione concentrations in



patients with ARDS (Bernard 1991, Bernard et al 1996, Laurent et al 1996). A direct antioxidant action for N-acetylcysteine in vivo is also supported by in vitro studies which indicated potent free radical scavenging activity (Aruoma et al 1989), and recent animal work has also shown that N-acetylcysteine may be capable of modulating the release of the protein Nuclear Factor  $\kappa$ B which has a pivotal role in initiating the systemic inflammatory response (Blackwell et al 1996). An immune modulating effect would be consistent with earlier animal work documenting suppression of TNF- $\alpha$  release by N-acetylcysteine (Peristeris et al 1992, Zhang et al 1994).

Although N-acetylcysteine is reported to decrease mortality in fulminant hepatic failure clinical studies in patients with ARDS and sepsis have equivocal results. In a prospective randomised controlled study in patients with mild to moderate acute lung injury N-acetylcysteine significantly reduced ventilator days and improved indices of oxygenation (Suter et al 1994). However the incidence of ARDS and mortality were not reduced. A small prospective double-blind controlled study also observed a non-significant trend towards a decrease in lung injury scores in the N-acetylcysteine-treated group in patients with established ARDS (Bernard et al 1997). Jepsen and colleagues (1992) prospectively randomised 66 patients with established ARDS to receive N-acetylcysteine or placebo infusions for 6 days. These authors were unable to demonstrate any improvement in oxygenation indices, ventilator requirement or mortality in the N-acetylcysteine group, and associated a significant anticoagulant effect with the drug. In another prospective randomised controlled trial Molnar et al (1998) studied the effect of N-acetylcysteine infusion, commenced following admission to the intensive care unit, in a mixed group of 23 critically ill patients who required one or two organ system support. They found no beneficial effect on organ function, intensive care unit stay or mortality in comparison with a matched control group. There was also no difference in total plasma antioxidant potential or microalbuminuria (an index of capillary permeability) between the groups although plasma antioxidant potential was normal in the majority of patients at study entry.

Free radical production is implicated in mediating tissue damage following reperfusion of previously ischaemic tissues (the ischaemia-reperfusion syndrome). Liver transplantation



is a situation where true pre-insult treatment with antioxidant drugs is feasible. Reactive oxygen species are generated following graft reperfusion during orthotopic liver transplantation (Bzeizi et al 1993, 1997), a time at which acute depletion of plasma antioxidants has been demonstrated (Goode et al 1994). Experimental work has suggested that N-acetylcysteine may reduce reperfusion injury in transplanted livers either through an antioxidant mechanism (Nakano et al 1995, Fukuawa 1995) or by improving blood flow within the graft (Koeppel et al 1996, Thies et al 1997). Steib and colleagues (1998) hypothesised that treatment with N-acetylcysteine prior to graft reperfusion may be beneficial in human liver transplantation. However, in a prospective randomised controlled study of 60 patients undergoing elective liver transplantation they were unable to demonstrate any clinical benefit from N-acetylcysteine started during the anhepatic phase. Similar findings were reported by Bromley et al (1995).

It is clear from this review of the literature that, if not via improved global oxygen kinetics, a possible beneficial therapeutic effect of N-acetylcysteine in critically ill human patients has a sound theoretical and experimental basis, but is unproven in clinical studies. Further work in this area is clearly warranted.

In chapter 4 the energy expenditure of patients with fulminant hepatic failure was investigated. This was considered of particular interest because of the many contrasting factors which may influence metabolic rate in this condition, in particular the massive loss of functioning liver cell mass which, in health, is metabolically highly active. The patients in this study were paralysed, sedated, and ventilated which made meaningful comparison with a control group problematic. It was therefore not surprising that predictive equations for estimating energy expenditure were of little value. Comparing patients with healthy control subjects indicated that energy expenditure is significantly elevated in fulminant hepatic failure despite the effects of paralysis and sedation on metabolic rate. This finding was confirmed from the comparison with patients studied during the anhepatic phase of liver transplantation. In health metabolic rate is determined primarily by lean body mass, and 20-25% of this is attributable to hepatic metabolism. The studies in chapter 4 indicated that alterations in liver metabolic rate *per se* are not the primary determinant of energy expenditure during fulminant hepatic failure. Instead, other systemic factors

predominate. Patients have the clinical features of the systemic inflammatory response syndrome which is characterised by hypermetabolism in other forms of critical illness. In the patients with fulminant hepatic failure TNF and IL-6 concentrations were elevated and it is likely that these, and other inflammatory factors, mediate the increase in energy expenditure in this condition. It was interesting that an acute phase protein response, as measured by C reactive protein concentrations, was present even though this is thought to require intact hepatic synthetic function. This may indicate residual synthetic function within the liver or perhaps an alternative source of acute phase proteins.

This study clearly indicates a significant increase in energy requirements in patients with fulminant hepatic failure. In other forms of critical illness the metabolic response to increased energy requirements includes marked increases in hepatic gluconeogenesis and lipolysis both of which are likely to be significantly impaired during fulminant hepatic failure. The combination of markedly increased glucose demand and reduced hepatic synthesis explains the frequent occurrence of hypoglycaemia in this condition.

In chapters 5-7 oxygen kinetics in patients undergoing liver transplantation were examined. Physiological studies during clinical liver transplantation are difficult because many factors influence the variables under consideration which can each change rapidly, in particular at the time of graft reperfusion. The approach used in this thesis was to average as many data points as possible for the periods of interest in order to measure as accurately as possible the true status of patients at particular time points or during particular periods. The use of a continuous cardiac output monitor was of particular value in this respect. In chapter 5 the changes in cardiovascular and gas exchange variables which occur following reperfusion were documented in detail. It was clear that a substantial increase in metabolic rate occurs at this time. This observation has been made by some previous authors many of whom have suggested this to be a valid marker of graft function. It is clear, however, that many factors influence metabolic rate at this time in addition to oxygen uptake by the graft, notably oxygen debt from the anhepatic period and the effect of pro-inflammatory mechanisms which accompany the ischaemia-reperfusion process.

Reperfusion is the time point at which most clinically relevant complications occur during liver transplantation, probably as a result of rapid cardiovascular, electrolyte, and acid-base alterations and from the release of undefined substances from the graft. In chapters 6 and 7 the effect of different surgical techniques on some of these variables was examined. In comparing the piggyback technique with venovenous bypass during the anhepatic phase it was found that cardiac output and oxygen consumption were higher with the piggyback technique. Changes in cardiac output following reperfusion were less marked with the piggyback technique. There was also the suggestion that acidaemia was reduced with this technique consistent with less tissue hypoxia. A significant difference between the groups was in preservation of body temperature which was better in the piggyback group. This was a small observational study which was not randomised and therefore potentially subject to bias. No conclusions can be made regarding outcome. It should progress to a formal randomised study of sufficient power to determine clinical benefit but, as is frequently the case in research of this nature, I suspect that a trial of this nature will never be performed. Despite these shortcomings it is a reasonable conclusion that, in those patients studied, the data indicate better overall metabolic stability with the piggyback technique.

Chapter 7 compared reperfusion via the portal vein and hepatic artery. A major consideration here was the contrast between the early and late complications of reperfusion and the fact that interventions might not benefit both concurrently. As with the previous chapter this study was observational and subject to potential bias with respect to randomisation, but the data indicated clear differences between the groups. With the portal vein oxygen uptake increased far more rapidly, but at a cost of greater acid-base disturbance and requirement for pharmacological cardiovascular support. The clinical implication of this finding is greater overall stability when the hepatic artery is used for reperfusion. Of concern is the possibility that, if most of the increase in oxygen consumption is attributable to graft uptake, oxygenation of the graft is less rapid with the hepatic artery. A future study should specifically compare early graft function with each technique of reperfusion.

Cardiovascular and neurological instability occur most frequently at reperfusion in

patients undergoing transplantation for fulminant hepatic failure. These patients are relatively infrequent, clinically complex, and therefore difficult to study. From the studies in this thesis it is an attractive hypothesis that optimal management includes the use of the piggyback technique, reperfusion via the hepatic artery, and an increase in minute ventilation immediately prior to reperfusion.

The most difficult patients to manage are frequently the most difficult to study. Critically ill patients with liver failure are amongst the most metabolically complex to manage. Few would disagree that the delivery and metabolism of oxygen are central to understanding the pathophysiology of critical illness. This thesis has attempted to address these issues in patients with liver failure on a whole body scale. Further understanding will require information on oxygen balance at an organ, tissue, and cellular level. This is the major challenge for future research in this area.

## REFERENCES

- Abraham E, Bland RD, Cobo JC, Schoemaker WC.  
Sequential cardiorespiratory patterns associated with outcome in septic shock. *Chest* 1984; 85:75-80.
- Aggarwal S, Kang Y, Freeman JA, Fortunato FL, Pinsky MR.  
Post reperfusion syndrome: cardiovascular collapse following hepatic reperfusion during liver transplantation. *Transplantation Proceedings* 1987; 19(Suppl. 3): 54-55.
- Albaladejo P, Jugan E, Descorps-Declare A, Jayais P, Ecoffey C.  
Whole body oxygen uptake is not a good indicator of liver allograft function following orthotopic liver transplantation. *European Journal of Anaesthesiology* 1994; 11: 201-206.
- Annat G, Viale J-P, Percival C, Froment M, Motin J.  
Oxygen delivery and uptake in the Adult Respiratory Distress Syndrome: Lack of a relationship when measured independently in patients with normal blood lactate concentrations. *Am Rev Respir Dis* 1986; 133:999-1001.
- Archie JP.  
Mathematical Coupling of Data: a common source of error. *Ann Surg* 1980; 193:296-303.
- Aruoma OI, Halliwell B, Hoey BM, Butler J.  
The antioxidant action of N-acetylcysteine: its reaction with hydrogen peroxide, hydroxyl radical, superoxide, and hypochlorous acid. *Free Radic Biol Med* 1989; 6:593-597.
- Astiz M, Rackow EC, Falk JL et al  
Oxygen delivery and consumption in patients with hyperdynamic septic shock. *Crit Care Med* 1987; 15:26-28.
- Astiz M, Rackow EC, Falk JL et al .  
Oxygen delivery and consumption in patients with hyperdynamic septic shock. *Crit Care Med* 1987; 15:26-28.
- Aukburg SJ, Geer RT, Wollman H, Neufeld GR.  
Errors in measurement of oxygen uptake due to anaesthetic gases. *Anesthesiology* 1985; 62:54-59.
- Bakker J, Coffernils M, Leon M, Gris P, et al.  
Blood lactate levels are superior to oxygen derived variables in predicting outcome in human septic shock. *Chest* 1991; 99:956-962.



Banda PW, Quart BD.

The use of N-acetylcysteine long after an acetaminophen overdose in mice. *Toxicol Lett* 1987; 36:89-94.

Bartlett RH, Dechet RE.

Oxygen kinetics: pitfalls in clinical research. *J Crit Care* 1990; 5: 77-80.

Barton R, Cerra FB

The hypermetabolism multiple organ failure syndrome. *Chest* 1989; 96:1153-1160.

Bateman DN, Woodhouse KW, Rawlins MD.

Adverse reactions to N-acetylcysteine. *Hum Toxicol* 1984; 3:393-398.

Baudouin SV, Howdle P, O'Grady JG, Webster NR.

Acute lung injury in fulminant hepatic failure following paracetamol poisoning. *Thorax* 1995; 50: 399-402.

Bauman PF, Smith TK, Bray TM.

The effect of dietary protein and sulfur amino acids on hepatic glutathione concentration and glutathione-dependent enzyme activities in the rat. *Can J Physiol Pharmacol* 1988; 66:1048-1052.

Beards SC, Edwards JD, Nightingale P.

The need for quality control in measurement of mixed venous oxygen saturation. *Anaesthesia* 1994; 49:886-888.

Beckett GJ, Donovan JW, Hussey AJ, Proudfoot AT, Prescott LF.

Intravenous N-acetylcysteine, hepatotoxicity, and plasma glutathione-S-transferase in patients with paracetamol overdose. *Hum Exp Toxicol* 1990; 9:183-186.

Belghiti J, Noun R, Sauvanet A, Durand F, Aschehoug J, Erlinger S, Benhamou JP, Bernuau J.

Transplantation for fulminant and subfulminant hepatic failure with preservation of portal and caval flow. *Brit J Surg* 1995; 82:986-989.

Bellamy MC, Galley HF, Webster NR.

Changes in inflammatory mediators during orthotopic liver transplantation. *British Journal of Anaesthesia* 1997; 79: 338-342.

Bernard GR, Lucht WD, Niedermeyer ME, Snapper JR, Ogletree ML, Brigham KL.

Effect of N-acetyl cysteine on the pulmonary response to endotoxin in the awake sheep and upon in vitro granulocyte function. *J Clin Invest* 1984; 73:1772-1784.

Bernard GR.

N-acetylcysteine in experimental and clinical acute lung injury. *Am J Med* 1991; 91(Suppl 3C):54-59.



Bernard GR, Wheeler AP, Arons MM, Morris PE, Paz HL, Russell JA, Wright PE; and The Antioxidant in ARDS Study Group.

A trial of antioxidants N-acetylcysteine and Procysteine in ARDS. *Chest* 1997; 112:164-172.

Bernuau J, Goudeau A, Poynard T, Dubois F, Lesage G, Yvonnet B, Degott C, Bezeaud A, Rueff B, Benhamou JP.

Multivariate analysis of prognostic factors in fulminant hepatitis. *Hepatology* 1986; 6:648-651.

Beutler E.

Nutritional and metabolic aspects of glutathione. *Ann Rev Nutr* 1989; 9:287-302.

Bhatt SB, Hutchinson RC, Tomlinson B, Oh TE, Mak M.

Effect of dobutamine on oxygen supply and uptake in healthy volunteers. *Brit J Anaesth* 1992; 69:298-303.

Bihari D, Gimson AES, Waterson M, Williams R.

Tissue hypoxia during fulminant hepatic failure. *Crit Care Med*. 1985; 13:1034-1039.

Bihari D, Smithies M, Gimson A, Tinker J.

The effect of vasodilation with prostacyclin on oxygen delivery and uptake in critically ill patients. *N Engl J Med* 1987; 317:397-403.

Bishop MH, Schoemaker WC, Appel PL, et al.

Prospective randomised trial of survivor values of cardiac index, oxygen delivery and oxygen consumption as resuscitation endpoints in severe trauma. *J Trauma* 1995; 38:780-787.

Bizouarn P, Blanloeil Y, Pinaud M.

Comparison between oxygen consumption calculated by Fick's principle and measured by indirect calorimetry. *Br J Anaesth* 1995; 75:719-23.

Blackwell TS, Blackwell TR, Holden EP, Christman BW, Christman JW.

In vivo antioxidant treatment suppresses nuclear factor- $\kappa$ B activation and neutrophilic lung inflammation. *J Immunol* 1996; 157:1630-1637.

Blackwell TS and Christman JW.

Sepsis and cytokines: current status. *Brit J Anaesth* 1996; 77:110-117.

Bland JM, Altman DG.

Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 8:307-310.

Bland JM, Altman DG.

Measurement error. *Brit Med J* 1996; 312:1654.

Blazka ME, Wilmer JL, Holladay SD, Wilson RE, Luster MI.

Role of proinflammatory cytokines in acetaminophen hepatotoxicity. *Toxicol Appl Pharmacol* 1995; 133:43-52.

Blei AT.

Cerebral edema and intracranial hypertension in acute liver failure: distinct aspects of the same problem. *Hepatology* 1991; 13:377-379.

Boesgaard S, Aldershvile J, Poulsen HE.

Preventive administration of intravenous N-acetylcysteine and development of tolerance to isosorbide dinitrate in patients with angina pectoris. *Circulation* 1992; 85:143-149.

Boldt J, Menges T, Wollbruck M, Hammermann H, Hempelmann G.

Is continuous cardiac output measurement using thermodilution reliable in the critically ill patient? *Crit Care Med* 1994; 22:1913-1918.

Boman G, Backer U, Larsson S, Melander B, Wahlander L.

Oral acetylcysteine reduces exacerbation rates in chronic bronchitis: report of a trial organised by the Swedish Society for Pulmonary Diseases. *Eur J Respir Dis* 1983; 64: 405-415.

Bonanomi L, Gazzaniga A.

Toxicological, pharmacokinetic and metabolic studies on acetylcysteine. *Eur J Respir Dis* 1980; 61(Suppl. 111):45-51.

Bone RC.

Sir Isaac Newton, sepsis, SIRS, and CARS. *Crit Care Med* 1996; 24:1125-1128.

Borgstrom L, Kagedal B, Paulsen O.

Pharmacokinetics of N-acetylcysteine in man. *Eur J Clin Pharmacol* 1986; 31:217-222.

Borrelli E, Roux-Lombard P, Grau GE, Girardin E, Ricou B, Dayer J-M, Suter PM.

Plasma concentrations of cytokines, their soluble receptors, and antioxidant vitamins can predict the development of multiple organ failure in patients at risk. *Crit Care Med* 1996; 24:392-397.

Bottiger BW, Sinner B, Motsch J, Bach A, Bauer H, Martin E.

Continuous versus intermittent cardiac output measurement during orthotopic liver transplantation. *Anaesthesia* 1997; 57: 207-214.

Boulanger BR, Nayman R, McLean RF, Phillips E, Rizoli SB.

What are the clinical determinants of early energy expenditure in critically injured patients? *J Trauma* 1994; 37:969-974.

Boyd O, Grounds M, Bennett D.

The dependency of oxygen consumption on oxygen delivery in critically ill postoperative patients is mimicked by variations in sedation. *Chest* 1992; 101:1619-1624.

Boyd O, Grounds RM, Bennett ED.

A randomised clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA* 1993; 270:2699-707.

Bracco D, Chiolerio R, Pasche O, Revelly JP.

Failure in measuring gas exchange in the ICU. *Chest* 1995; 107:1406-1410.

Brent BN, Matthay R, Mahler DA et al

Relationship between oxygen uptake and oxygen transport in stable patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1984; 129:682-686.

Bridgeman MME, Marsden M, Selby C, Morrison D, MacNee W.

Effect of N-acetyl cysteine on the concentrations of thiols in plasma, bronchoalveolar lavage fluid, and lung tissue. *Thorax* 1994; 49:670-675.

Bromley PN, Cottam SJ, Hilmi I, Tan KC, Heaton N, Ginsburg R, Potter DR.

Effects of intraoperative N-acetylcysteine in orthotopic liver transplantation. *Brit J Anaesth* 1995; 75:352-354.

Burgunder JM, Varriale A, Lauterburg BH.

Effect of N-acetylcysteine on plasma cysteine and glutathione following paracetamol administration. *Eur J Clin Pharmacol* 1989; 127:127-131.

Bursztein S, Saphar P, Glaser P, Taitelman U, Myttenaere S, Nedey R.

Determination of energy metabolism from respiratory function alone. *J Appl Physiol* 1977; 42:117-119.

Bursztein S, Elwyn DH, Askanazi J, Kinney JM.

Energy Metabolism, Indirect calorimetry, and Nutrition. Chapter 2: The theoretical framework of indirect calorimetry and energy balance. Williams & Wilkins, Baltimore, Maryland 1989.

Bzeizi K, Soutar A, Hayes P.

Free radical production following vascular reperfusion. *Lancet* 1993; 342:61-62.

Bzeizi K, Dawkes R, Dodd N, Plevris J, Hayes P.

Graft dysfunction following liver transplantation. Role of free radicals. *Journal of Hepatology* 1997;26:69-74..

Bzeizi KI, Jalan R, Plevris JN, Hayes PC.

Primary graft dysfunction after liver transplantation: from pathogenesis to prevention. *Liver Transplantation and Surgery* 1997;3:136-148.

Cain SM.

Peripheral oxygen uptake in health and disease. Clin Chest Med 1983; 4:139-

Cain SM, Curtis SE.

Experimental models of pathologic supply dependency. Crit Care Med 1991; 19:603-612.

Canalese J, Gimson AES, Davis C, Mellon PJ, Davis M, Williams R.

Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure. Gut 1982; 23:625-629.

Carlile PV, Gray BA.

Effect of opposite changes in cardiac output and arterial  $pO_2$  in the relation between mixed venous  $pO_2$  and oxygen transport. Am Rev Respir Dis 1989; 140:891-898.

Carton EG, Plevak DJ, Kranner PW, Rettke SR, Geiger HJ, Coursin DB.

Perioperative care of the liver transplant patient: part 2. Anesthesia and Analgesia 1994; 78: 382-399.

Chan TYK, Critchley AJH.

Adverse reactions to intravenous N-acetylcysteine in chinese patients with paracetamol (acetaminophen) poisoning. Hum Exp Toxicol 1994; 13:542-544.

Cheema SPS, Hughes A, Webster NR, Bellamy MC.

Cardiac function during orthotopic liver transplantation with venovenous bypass. Anaesthesia 1995; 50: 776-778.

Chiolero R, Revelly J-P, Tappy L.

Energy metabolism in sepsis and injury. Nutrition 1997; 13(Suppl):45S-51S.

Cotgreave IA, Moldeus P.

Methodologies for the analysis of reduced and oxidised N-acetylcysteine in biological systems. Biopharm Drug Disp 1987; 8:365-375.

Cowley HC, Bacon PJ, Goode H, Webster NR, Jones JG, Menon DK.

Plasma antioxidant potential in severe sepsis: a comparison of survivors and nonsurvivors. Crit Care Med 1996; 24:1179-1183.

Cuthbertson DP.

Post-shock metabolic response. Lancet 1942; i:433-437

D'Alessio D, Kavle C, Mozzoli MA et al.

Thermic effects of food in lean and obese men. J Clin Invest 1988; 81: 1781-

Danek SJ, Lynch JP, Weg JG, Dantzker DR.

The dependence of oxygen uptake on oxygen delivery in the adult respiratory distress syndrome. Am Rev Respir Dis 1980; 122:387-395.

Davenport A, Will EJ, Davidson AM.

Paradoxical increase in arterial hydrogen ion concentration in patients with hepatorenal failure given lactate-based fluids. *Nephrol Dial Transplant* 1990; 5:342-346.

Davenport A, Will EJ, Davidson AM.

Effect of renal replacement therapy on patients with combined acute renal and fulminant hepatic failure. *Kidney Int* 1993(a); 43(Suppl. 41):S245-S251.

Davenport A, Will EJ, Davidson AM.

Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic failure and renal failure. *Crit Care Med* 1993(b); 21:328-338.

De Backer D, Berre J, Zhang H, Kahn RJ, Vincent J-L.

Relationship between oxygen uptake and oxygen delivery in septic patients: effects of prostacyclin versus dobutamine. *Crit Care Med* 1993; 21:1658-1664.

De Backer D, Moraine J-J, Berre J, et al.

Effects of dobutamine on oxygen consumption in septic patients. *Am J Respir Crit Care Med* 1994; 150:95-100.

De Wolf AM, Begliomini B, Gasior TA, Kang Y, Pinsky MR.

Right ventricular function during orthotopic liver transplantation. *Anesth Analg* 1993; 76:562-568.

Deneke SM, Fanberg BL.

Regulation of cellular glutathione. *Am J Physiol* 1989; 257:L163-L173.

Devlin J, Ellis AE, McPeake J, Heaton N, Wendon JA, Williams R.

N-acetylcysteine improves indocyanine green extraction and oxygen transport during hepatic dysfunction. *Crit Care Med* 1997; 25:236-242.

Dhainaut JF, Edwards JD, Grootendorst AF, Nightingale P, Pinsky MR, Reinhart K, Schoemaker WC, Vincent J-L.

Practical aspects of oxygen transport: conclusions and recommendations of the Roundtable Conference. *Intensive Care Med* 1990; 16[Suppl 2]:S179-180.

Doblar DD, Lim YC, Frenette L, Poplawski S, Ranjan D, Ronderos J.

The effect of acute hypocapnia on middle cerebral artery transcranial Doppler velocity during orthotopic liver transplantation: changes at reperfusion. *Anesth Analg* 1995; 80:1194-1198.

Ede RJ, Gimson AES, Bihari D, Williams R.

Controlled hyperventilation in the control of cerebral oedema in fulminant hepatic failure. *J Hepatol* 1986; 2:43-51



- Edwards JD, Brown GCS Nightingale P, et al.  
Use of survivors' cardiorespiratory values as therapeutic goals in septic shock. *Crit Care Med* 1989; 17:1098-1103.
- Ensinger H, Weichel T, Lindner K-H, Gruenert A, Ahnefeld FW.  
Effects of norepinephrine, epinephrine, and dopamine infusions on oxygen consumption in volunteers. *Crit Care Med* 1993; 21:1502-1508.
- Ensinger H, Weichel T, Lindner K-H, Gruenert A, Georgieff M.  
Are the effects of noradrenaline, adrenaline and dopamine infusions on  $\text{VO}_2$  and metabolism transient? *Intensive Care Med* 1995; 21:50-56.
- Esen F, Telci L, Cakar N, et al.  
Evaluation of gastric intramucosal pH measurements with tissue oxygenation indices in patients with severe sepsis. *Clinical Intensive Care* 1996; 7:180-189
- Estrin JA, Belani KG, Ascher NL, Lura D, Payne W, Najarian JS.  
Hemodynamic changes on clamping and unclamping of major vessels during liver transplantation. *Transplantation Proceedings* 1989; 21: 3500-3505.
- Ferenci P.  
Brain dysfunction in fulminant hepatic failure. *J Hepatol* 1994; 21:487-490.
- Ferrannini E.  
The theoretical bases of indirect calorimetry: a review. *Metabolism* 1988; 37:287-301.
- Figueras J, Sabate A, Fabregat J, Torras J, Drudis R, Rafecas A, Dalmau A, Bartolome C, Jaurieta E.  
Hemodynamics during the anhepatic phase in orthotopic liver transplantation with vena caval preservation: a comparative study. *Transplant Proc* 1993; 25:2588-2589.
- Flanagan RJ, Meredith TJ.  
Use of N-acetylcysteine in clinical toxicology. *Am J Med* 1991; 91(Suppl 3C):131-139.
- Fleming A, Bishop M, Schoemaker W et al.  
Prospective trial of supranormal values as goals of resuscitation in severe trauma. *Arch Surg* 1992; 127:1175-1181.
- Frankenfield DC, Wiles CE, Bagley S, Siegal JH.  
Relationships between resting and total energy expenditure in injured and septic patients. *Crit Care Med* 1994; 22:1796-1804.
- Fukuawa K, Emre S, Senyuz O, Acarli K, Schwartz ME, Miller CM.  
N-acetylcysteine ameliorates reperfusion injury after warm hepatic ischaemia. *Transplantation* 1995; 59:6-9.



Fung H-L, Chong E, Kowaluk E, Hough K, Kakemi M.  
Mechanisms for the pharmacologic interaction of organic nitrates with thiols.  
Existence of an extracellular pathway for the reversal of nitrate vascular tolerance by N-acetylcysteine. *J Pharm Exp Ther* 1988; 245:524-530.

Gabel RA

Algorithms for calculating and correcting blood-gas and acid-base variables. *Respir Physiol* 1980; 42:211-232.

Gadek JE, Pacht ER.

The interdependence of lung antioxidants and antiprotease defence in ARDS. *Chest* 1996; 110:273S-277S.

Galley HF, Howdle PD, Walker BE, Webster NR.

The effects of intravenous antioxidants in patients with septic shock. *Free Rad Biol Med* 1997; 23:768-774

Ganong WF.

Review of medical physiology. Fifteenth edition. East Norwalk, CT: Appleton and Lange, Connecticut, 1991: 563.

Gasman JD, Ruoss SJ, Fishman RS, et al.

Hazards with both determining and utilising oxygen consumption measurements in the management of critically ill patients. *Crit Care Med* 1996; 24:6-9.

Gattinoni L, Brazzi L, Pelosi P et al. A

Trial of goal-oriented hemodynamic therapy in critically ill patients. *N Engl J Med* 1995;333 1025-32.

Gimson AES.

Fulminant and late onset hepatic failure. *Brit J Anaesth* 1996; 77:90-98.

Goldie AS, Fearon KCH, Ross JA, Barclay R, Jackson RE, Grant IS, Ramsay G, Blyth AS, Howie JC.

Natural cytokine antagonists and endogenous antiendotoxin core antibodies in sepsis syndrome. *JAMA* 1995; 274:172-177.

Goode HF, Webster NR.

Free radicals and antioxidants in sepsis. *Crit Care Med* 1993; 21:1770-1776.

Goode HF, Webster NR, Howdle PD, Leek JP, Lodge JPA, Sadek SA, Walker BE.

Reperfusion injury, antioxidants and hemodynamics during orthotopic liver transplantation. *Hepatology* 1994; 19:354-359.

Goode HF, Cowley HC, Walker BE, Howdle PD, Webster NR.

Decreased antioxidant status and increased lipid peroxidation in patients with septic shock and secondary organ dysfunction. *Crit Care Med* 1995; 23:646-651.

Green CJ, Frazer RS, Underhill S, Maycock P, Fairhurst JA, Campbell IT.  
Metabolic effects of dobutamine in normal man. *Clin Sci* 1993; 82:77-83.

Grosse H, Lobbes W, Frambach M, Ringe B, Barthels M.  
Influence of high dose aprotinin on hemostasis and blood requirement in orthotopic liver transplantation. *Seminars Thromb Hemostas* 1993; 19:302-305.

Gubernatis G, Bornscheuer A, Taki Y, Farle M, Lubbe N, Yamaoka Y, Beneking M, Burdelski M, Oellerich M.  
Total oxygen consumption, ketone body ratio and a special score as early indicators of irreversible liver allograft dysfunction. *Transplantation Proceedings* 1989; 21: 2279-2281.

Gunning T, Brajtford D, Valek TR et al.  
Intracranial hypertension following graft reperfusion. *Anesthesiology* 1990; 72:391-392.

Hanique G, Dugernier T, Laterre PF, Dougnac A, Roeseler J, Reynaert MS.  
Significance of pathologic oxygen supply dependency in critically ill patients: comparison between measured and calculated methods. *Intensive Care Med*. 1994a; 20:12-18.

Hanique G, Dugernier T, Laterre PF, et al:  
Evaluation of oxygen uptake and delivery in critically ill patients: a statistical reappraisal. *Intensive Care Med* 1994b; 20:19-26.

Hankeln KB, Senker R, Schwarten JU et al.  
Evaluation of prognostic indices based on haemodynamic and oxygen transport variables in shock patients with adult respiratory distress syndrome. *Crit Care Med* 1987; 15:1-7.

Hannemann L, Reinhart K, Meier-Hellmann A, Bredle DL.  
Prostacyclin in septic shock. *Chest* 1994; 105:1504-1510.

Harris JA, Benedict FG.  
A biometric study of basal metabolism in man. Washington, DC, Carnegie Institute, 1919:1-266.

Harrison P, Keays R, Bray G, Alexander G, Williams R.  
Improved outcome in paracetamol-induced fulminant hepatic failure following late administration of N-acetylcysteine. *Lancet* 1990; 335: 1572-1573.

Harrison PM, Wendon JA, Gimson AES, Alexander GJM, Williams R.  
Improvement by acetylcysteine of haemodynamics and oxygen transport in fulminant hepatic failure. *N Eng J Med* 1991; 324: 1852-1857.

Harrison P, Wendon J, Williams R.  
Evidence of increased guanylate cyclase activation by acetylcysteine in fulminant hepatic failure. *Hepatology* 1996; 23:1067-1072.

Hawker F.

The Liver. Chapter 3: Fulminant Hepatic Failure. WB Saunders. London 1993.

Hayes MA, Yau EHS, Timmins AC, Hinds CJ, Watson D.

Response of critically ill patients to treatment aimed at achieving supranormal oxygen delivery and consumption: relationship to outcome. *Chest* 1993; 103:886-895.

Hayes MA, Timmins AC, Yau EHS et al.

Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; 330:1717-1722.

Hayes MA, Timmins AC, Yau EHS, Palazzo M, Watson D, Hinds CJ.

Oxygen transport patterns in patients with sepsis syndrome or septic shock: influence of treatment and relationship to outcome. *Crit Care Med* 1997; 25: 926-936.

Henneberg S, Soderberg D, Groth T, et al.

Carbon dioxide production during mechanical ventilation. *Crit Care Med* 1987; 15:8-13.

Heinrich PC, Castell JV, Andus T.

Interleukin-6 and the acute phase response. *Biochem J* 1990; 265:621-636.

Heyland DK, Cook DJ, King D, et al.

Maximising oxygen delivery in critically ill patients: a methodological appraisal of the evidence. *Crit Care Med* 1996; 24:517-524.

Hinds C, Watson D.

Manipulating hemodynamics and oxygen transport in critically ill patients. *N Engl J Med* 1995; 333:1074-1075.

Hirst RP, Slee TA, Lam AM.

Changes in cerebral blood flow velocity after release of intraoperative tourniquets in humans: a transcranial Doppler study. *Anesth Analg* 1990; 70:503-510.

Holdiness MR, Morgan LR, Gillen LE.

High performance liquid chromatographic determination of N-acetylcysteine in human serum following acetaminophen overdosage. *J Chromatogr* 1986; 382:99-106.

Horowitz JD, Henry CA, Syrjanen ML, Louis WJ, Fish RD, Antman EM, Smith TW.

Nitroglycerine/N-acetylcysteine in the management of unstable angina pectoris. *Eur Heart J* 1988; 9(Suppl A):95-100.

Hotchkiss RS, Karl IE.

Reevaluation of the role of cellular hypoxia and bioenergetic failure in sepsis. *JAMA* 1992; 267:1503-1510.

Howard T.

Piggyback liver transplantation with temporary portocaval shunting. Liver transplantation and surgery 1997; 5(Suppl1):S40.

Humer MF, Phang PT, Friesen BP, Allard MF, Goddard CM, Walley KR.

Heterogeneity of gut capillary transit times and impaired gut oxygen extraction in endotoxaemic pigs. J Appl Physiol 1996; 81:895-904.

Izumi S, Hughes RD, Langley PG, Pernambuco JR, Williams R.

Extent of the acute phase response in fulminant hepatic failure. Gut 1994; 35:982-986.

Jalan R, Plevris J, Jalan RA, Finlayson NCF, Hayes PC.

A pilot study of indocyanine green clearance as early predictor of graft function. Transplantation 1994; 58:196-200.

Jepsen S, Herlevsen P, Knudsen P, Bud MI, Klausen N-O.

Antioxidant treatment with N-acetylcysteine during adult respiratory distress syndrome: A prospective, randomised, placebo-controlled study. Crit Care Med 1992; 20:918-923.

Johansson M, Westerlund D.

Determination of N-acetylcysteine, intact and oxidised in plasma by column liquid chromatography and post-column derivatization. J Chromatogr 1986; 385:343-356.

Jolliet P, Thorens JB, Nicod L, et al.

Relationship between pulmonary oxygen consumption, lung inflammation, and calculated venous admixture in patients with acute lung injury. Intensive Care Med 1996; 22:277-285.

Kang YG, Freeman JA, Aggarwal S, DeWolf AM.

Hemodynamic instability during liver transplantation. Transplant Proc 1989; 21:3489-3492.

Kaufman BS, Rackow EC, Falk JA.

The relationship between oxygen delivery and consumption during fluid resuscitation of hypovolaemic and septic shock. Chest 1984; 85:336-340.

Keays R, Harrison PM, Wendon JA, Forbes A, Gove C, Alexander GJM, Williams R.

Intravenous N-acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. BMJ 1991; 303: 1026-1029.

Kindscher J, Hutchinson M, Levine J.

Is the ratio of venovenous bypass flow to cardiac output important during orthotopic liver transplantation? Transplant Proc 1993; 25:1824-1825.

Koeppel TA, Lehmann TG, Thies JC, Gehrcke R, Gebhard M-M, Herfarth C, Otto G, Post S.

Impact of N-acetylcysteine on the hepatic microcirculation after orthotopic liver transplantation. *Transplantation* 1996; 61:1397-1402.

Komatsu T, Shibutani K, Okamoto K, Kumar V, Kubal K, Sanchala V, Lees DE. Critical level of oxygen delivery after cardiopulmonary bypass. *Crit Care Med* 1987; 15:194-197.

Kreisberg RA.

Lactate homeostasis and lactic acidosis. *Ann Int Med* 1980; 92:227-37.

Kreymann G, Grosser S, Buggisch P, Gottschall C, Matthaei S, Greten H.

Oxygen consumption and resting metabolic rate in sepsis, sepsis syndrome, and septic shock. *Crit Care Med* 1993; 21: 1012-1019.

Krowka MJ.

Pathophysiology of arterial hypoxemia in advanced liver disease. *Liver Transplantation and Surgery* 1996; 2: 308-312.

Laurent T, Markert M, Feihl F, Schaller M-D, Perret C.

Oxidant-antioxidant balance in granulocytes during ARDS: Effect of N-acetylcysteine. *Chest* 1996; 109:163-166.

Leach RM, Treacher DF.

Oxygen Transport: the relationship between oxygen delivery and consumption. *Thorax* 1992; 47:971-978.

Lee WM.

Acute liver failure. *Am J Med* 1994; 96(Suppl 1A):3S-9S.

Leff JA, Wilke CP, Hybertson BM, Shanley PF, Beehler CJ, Repine JE.

Postinsult treatment with N-acetyl-L-cysteine decreases IL-1 induced neutrophil influx and lung leak in rats. *Am J Physiol* 1993; 265:L501-L506.

Lewis PA, Woodward AJ, Maddock J.

High performance liquid chromatographic assay for N-acetylcysteine in plasma and urine. *J Pharm Sci* 1984; 73:996-998.

Lewis PA, Woodward AJ, Maddock J.

Improved method for the determination of N-acetylcysteine in human plasma by high performance liquid chromatography. *J Chromatogr* 1984; 311:170-175.

Lidofsky SD, Bass NM, Prager MC, Washington DE, Read AE, Wright TL, Ascher NL, Roberts JP, Scharschmidt BF, Lake JR.

Intracranial pressure monitoring and liver transplantation for fulminant hepatic failure. *Hepatology* 1992; 16:1-7.



Lidofsky SD.

Liver Transplantation for fulminant hepatic failure. *Gastroenterology Clinics North America* 1993; 22:257-269.

Light RB.

Intrapulmonary oxygen consumption in experimental pneumococcal pneumonia. *J Appl Physiol* 1988; 64:2490-2495.

MacIntyre P, Pavlin E, Dwersteg J.

Effect of meperidine on oxygen consumption, carbon dioxide production and respiratory gas exchange in postanesthesia shivering. *Anesth Analg* 1987; 66: 751

MacNee W, Bridgeman MME, Marsden M, Drost E, Lannan S, Selby C, Donaldson K.

The effect of N-acetylcysteine and glutathione on smoke-induced changes in lung phagocytes and epithelial cells. *Am J Med* 1991; 91(Suppl. C):60S-66S.

Mant TGK, Tempowski JH, Volans GN, Talbot JCC.

Adverse reaction to N-acetylcysteine and effects of overdose. *BMJ* 1984; 289:217-219.

Manthous CA, Hall JB, Olson D, Singh M, Chatila W, Pohlman A, Kushner R, Schmidt GA, Wood LDH.

Effect of cooling on oxygen consumption in febrile critically ill patients. *Am J Respir Crit Care Med* 1995a; 151:10-14.

Manthous CA, Hall JB, Kushner R, Schmidt GA, Russo G, Wood LDH.

The effect of mechanical ventilation on oxygen consumption in critically ill patients. *Am J Respir Crit Care Med* 1995b; 151:210-204.

Makita K, Nunn JF, Royston B.

Evaluation of metabolic measuring instruments for use in critically ill patients. *Crit Care Med* 1990; 18:638-644.

Makk L, McClave S, Creech P, Johnson DR, Short AL, Whellow NL, Priddy FS, Sexton LK, Simpson P.

Clinical application of the metabolic cart to the delivery of total parenteral nutrition. *Crit Care Med* 1990; 18: 1320-1327.

Marecaux G, Pinsky MR, Dupont E, Kahn RJ, Vincent J-L.

Blood lactate levels are better prognostic indicators than TNF and IL-6 levels in patients with septic shock. *Intensive Care Med* 1996; 22:404-408

Marik PE, Kaufman D.

The effects of neuromuscular paralysis on systemic and splanchnic oxygen utilisation in mechanically ventilated patients. *Chest* 1996;109:1038-1042.



Meister A.

New developments in glutathione metabolism and their potential application to therapy. *Hepatology* 1984; 4:739-742.

Meister A.

Glutathione metabolism and its selective modification. *J Biol Chem* 1988; 263:17205-17208.

Merritt WT, Beattie C, Peck R, et al.

Vena caval pressure gradients during liver transplantation. *Transplantation* 1990; 50:336-338.

Meyer T, Buhl R, Kampf S, Magnussen H.

Intravenous N-acetylcysteine and lung glutathione of patients with pulmonary fibrosis and normals. *Am J Respir Crit Care Med* 1995; 152:1055-1060.

Miners JO, Drew R, Birkett OJ.

Mechanism of action of paracetamol protective agents in mice in vivo. *Biochem Pharmacol* 1984; 33:2995-3000.

Mitchell EA, Elliot RB.

Controlled trial of N-acetylcysteine in cystic fibrosis. *Aust Paediatr J* 1982; 18:40-42.

Mitsuo T, Yukioka T, Matsuda H, et al.

Continuous cardiac output measurement in hyperdynamic critically ill patients. *Crit Care Med* 1995; 23, No. 1 (Suppl.) A135

Miyata T, Yokoyama I, Todo S, Tzakis A, Selby R, Starzl TE.

Endotoxaemia, pulmonary complications, and thrombocytopenia in liver transplantation. *Lancet* 1989; 1:189-191.

Modig J, Sandin R.

Haematological, physiological and survival data in a porcine model of adult respiratory distress syndrome induced by endotoxaemia: effects of treatment with N-acetylcysteine. *Acta Chir Scand* 1987; 154:169-177.

Mohsenifar Z, Amin D, Jasper AC et al.

Dependence of oxygen consumption on oxygen delivery in patients with chronic congestive heart failure. *Chest* 1987; 92:447-450.

Molnar Z, Mackinnon KL, Shearer E, Lowe D, Watson ID.

The effect of N-acetylcysteine on total serum antioxidant potential and urinary albumin excretion in critically ill patients. *Intensive Care Med* 1998; 24:230-235.

- Moore FD. Bodily changes in surgical convalescence. I.  
The normal sequence-observations and interpretations. *Ann Surg* 1953; 137:289-315.
- Morgan LR, Holdiness MR, Gillen LE.  
N-acetylcysteine: its bioavailability and interactions with ifosfamide metabolites.  
*Semin Oncol* 1983; 10(Suppl. 1):56-61
- Mullen KD, Martin JV, Mendelson WB, Bassett ML, Jones EA.  
Could an endogenous benzodiazepine ligand contribute to hepatic encephalopathy?  
*Lancet* 1998; i:457-459.
- Munoz SJ, Robinson M, Northrup B, Bell R, Moritz M, Jarrell B, Martin P, Maddrey WC.  
Elevated intracranial pressure and tomography of the brain in fulminant hepatic failure. *Hepatology* 1991; 13:209-212.
- Munro HM, Wood CE, Taylor BL, et al:  
Continuous invasive cardiac output monitoring - the Baxter/Edwards Critical-Care Swan Ganz Intellicath and Vigilance system. *Clinical Intensive Care* 1994; 5:52-55.
- Murray JF, Matthay MA, Luce JM, Flick MR.  
An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; 138:720-723.
- Myburgh JA, Webb RK, Worthley LIG.  
Ventilation/perfusion indices do not correlate with the difference between oxygen consumption measured by the Fick principle and metabolic monitoring systems in critically ill patients. *Crit Care Med* 1992; 20:479-482.
- Nakano H, Boudjema K, Alexandre E, Imbs P, Chenard MP, Wolf P, et al.  
Protective effects of N-acetylcysteine on hypothermic ischaemia-reperfusion injury of rat liver. *Hepatology* 1995; 22:539-545.
- Nasraway S, Klein R, Spencer T et al.  
Haemodynamic correlates of outcome in patients undergoing orthotopic liver transplantation: evidence for early postoperative myocardial depression. *Chest* 1995; 107:218-224.
- Nelson DP, Samsel RW, Wood LDH, Schumacker PT.  
Pathological supply dependency of systemic and intestinal O<sub>2</sub> uptake during endotoxemia. *J Appl Physiol* 1988; 64:2410-2419.
- Nishikawa T, Dohi S.  
Errors in the measurement of cardiac output by thermodilution. *Canadian Journal of Anaesthesia* 1993; 40: 142-153.

Nunn JF.

Applied Respiratory Physiology 2nd Edition. London: Butterworths, 1977;334-374.

Nunn JF.

Pulmonary oxygen consumption. Intensive Care Med 1996; 22:275-76.

O'Grady JG, Alexander GJM, Hallyar KM, Williams R.

Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989; 97:439-445.

Olsson B, Johansson M, Gabrielsson J, Bolme P.

Pharmacokinetics and bioavailability of reduced and oxidised N-acetylcysteine. Eur J Clin Pharmacol 1988; 34:77-82.

Oudemans-van Straaten HM, Scheffer GJ, Eysman L, et al.

Oxygen consumption after cardiopulmonary bypass-implications of different measuring methods. Intensive Care Med 1993; 19:105-110.

Oudemans-van Straaten HM, Jansen PGM, te Velthuis H, Beenackers ICM, Stoutenbeek CP, van Deventer SJH, Sturk A, Eysman L, Wildevuur CRH.

Increased oxygen consumption after cardiac surgery is associated with the inflammatory response to endotoxaemia. Intensive Care Med 1996; 22:294-300.

Parker D, White JP, Paton D, Routledge PA.

Safety of late N-acetylcysteine treatment in paracetamol poisoning. Hum Exp Toxicol 1990; 9:25-27.

Parrillo JE.

Pathogenetic mechanisms of septic shock. New Engl J Med 1993; 328:1471-1477.

Peake SL, Moran JL, Leppard PI.

N-acetyl-L-cysteine depresses cardiac performance in patients with septic shock. Crit Care Med 1996; 24:1302-1310.

Peristeris P, Clark BD, Gatti S, Faggioni R, Mantovani A, Mengozzi M, Orencole SF, Sironi M, Ghezzi O.

N-acetylcysteine and glutathione as inhibitors of tumour necrosis factor production. Cell Immunol 1992; 140:390-399.

Phang PT, Rich T, Ronco J.

A validation and comparison study of two metabolic monitors. JPEN 1990; 14:259-261.

Phang PT, Cunningham KF, Ronco JJ, Wiggs BR, Russell JA.

Mathematical coupling explains dependence of oxygen consumption on oxygen delivery in ARDS. Am J Respir Crit Care Med. 1994; 150:318-323.

Philips BJ, Armstrong IR, Pollock A, Lee A. Cerebral blood flow and metabolism in patients with chronic liver disease undergoing liver transplantation. *Hepatology* 1998; 27:369-376.

Pinsky MR.

The meaning of cardiac output. *Intensive Care Med* 1990; 16:415-417.

Pinsky MR.

Beyond global oxygen supply-demand relations: in search of measures of dysoxia. *Intensive Care Med.* 1994; 20:1-3.

Poulin MJ, Liang P-J, Robbins PA.

Dynamics of the cerebral blood flow response to step changes in end-tidal PCO<sub>2</sub> and PO<sub>2</sub> in humans. *Journal of Applied Physiology* 1996; 81: 1084-1095.

Poulsen HE, Vilstrup H, Almdal T, Dalhoff K.

No net splanchnic release of glutathione in man during N-acetylcysteine infusion. *Scand J Gastroenterol* 1993; 28:408-412.

Powers SR, Mannal R, Neclerio et al .

Physiological consequences of positive end expiratory pressure (PEEP) ventilation. *Ann Surg* 1973; 178:265-272.

Prescott LF, Park J, Ballantyne A, Adriaenssens P, Proudfoot AT.

Treatment of paracetamol (acetaminophen) poisoning with N-acetylcysteine. *Lancet* 1977; 2:432-434.

Prescott LF, Illingworth RN, Critchley JAJH, Stewart MJ, Adam RD, Proudfoot AT.

Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. *BMJ* 1979; ii:1097-1100.

Prescott LF, Donovan JW, Jarvie DR, Proudfoot AT.

The disposition and kinetics of intravenous N-acetylcysteine in patients with paracetamol overdose. *Eur J Clin Pharmacol* 1989; 37:501-506.

Ramsøe K, Buch Andreasen P, Ranek L.

Functioning liver cell mass in uncomplicated and fulminant acute hepatitis. *Scand J Gastroenterol* 1980; 15:65-72.

Reinhart K, Spies CD, Meier-Hellmann A, Bredle DL, Hannemann L, Specht M, Schaffartzik W.

N-acetylcysteine preserves oxygen consumption and gastric mucosal pH during hyperoxic ventilation. *Am J Respir Crit Care Med* 1995; 151:773-779.

Riano D, Perez-Cerda F, Martinez P, Davila P, Cisneros C, Moreno E, Segovia D, Bonet H, Del Campo I.

Why does mixed venous oxygen saturation fall at the moment of graft reperfusion in liver transplantation? *Transplant Proced* 1991; 23:1962-1963.

Rodenstein D, De Coster A Gazzaniga A.

Pharmacokinetics of oral acetylcysteine: absorption, binding and metabolism in patients with respiratory disorders. *Clin Pharmacokinet* 1978; 3: 247-254.

Rolando N, Harvey F, Brahm J, Philpott-Howard J, Alexander G, Gimson A, Casewell M, Fagan E, Williams R.

Prospective study of bacterial infection in acute liver failure: an analysis of 50 patients. *Hepatology* 1990; 11:49-53.

Ronco JJ, Phang PT:

Validation of an indirect calorimeter to measure oxygen consumption in the ranges seen in critically ill patients. *J Crit Care* 1991; 6:36-41.

Ronco JJ, Phang PT, Wiggs P, Walley KR, Fenwick JC, Russell JA.

Oxygen consumption is independent of increases in oxygen delivery in severe adult respiratory distress syndrome. *Am Rev Respir Dis.* 1991; 143:1267-1273.

Ronco JJ, Fenwick JC, Wiggs BR, Phang PT, Russell JA, Tweeddale MG.

Oxygen consumption is independent of increases in oxygen delivery by dobutamine in septic patients who have normal or increased plasma lactate. *Am Rev Respir Dis* 1993; 147:25-31.

Ronco JJ, Fenwick JC, Tweeddale MG, Wiggs BR, Phang PT, Cooper DJ, Cunningham KF, Russell JA Walley KR.

Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA* 1993; 270:1724-1730.

Rothen HU, Sporre B, Engberg G, Wegenius G, Reber A, Hedenstierna G.

Prevention of atelectasis during general anaesthesia. *Lancet* 1995; 345: 1387-1391.

Roza AM, Shizgal HM.

The Harris Benedict equation reevaluated: resting energy requirements and the body cell mass. *Am J Clin Nutr* 1984; 40:168-182.

Russell JA, Ronco JJ, Lockhat D et al.

Oxygen delivery and consumption and ventricular preload are greater in survivors than in nonsurvivors of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1990; 141:659-665.

Russell SH, Bokos J, Freeman JW.

Oxygen consumption of the transplanted liver and its correlation with whole body oxygen consumption. *Brit J Anaesth* 1995; 74(Suppl 1):A178

Russell JA, Phang PT.

The oxygen delivery/consumption controversy: Approaches to management of the critically ill. *Am J Respir Crit Care Med* 1994; 149:533-537.

Ruttiman Y, Schutz Y, Jequier E, Lemarchand T, Chioler R.

Thermogenic and metabolic effects of dopamine in healthy men. *Crit Care Med* 1991; 19:1030-1036.

Schneeweiss B, Pammer J, Ratheiser K, Schneider B, Madl C, Kramer L, Kranz A, Ferenci P, Druml W, Grimm G, Lenz K, Gangl A.

Energy metabolism in acute hepatic failure. *Gastroenterology* 1993; 105:1515-1521.

Schneider F, Lutun P, Boudjema K, Wolf P, Tempe J-D.

In vivo evidence of enhanced guanylate cyclase activation during the hyperdynamic circulation of acute liver failure. *Hepatology* 1994; 19:38-44.

Schoemaker WC.

Cardiorespiratory patterns of surviving and nonsurviving postoperative patients. *Surg Obst Gynaecol* 1972; 134:810-814.

Schoemaker WC, Montgomery ES, Kaplan ES, Elwyn DH.

Physiologic patterns in surviving and non surviving shock patients. *Arch Surg* 1973; 106: 630-636.

Schoemaker WC, Appel PL, Waxman K, Schwartz S, Chang P.

Clinical trial of survivors cardiorespiratory patterns as clinical goals in critically ill postoperative surgical patients. *Crit Care Med* 1982; 10:398-403.

Schoemaker WC, Appel PL, Kram HB, et al.

Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988; 94: 1176-86.

Schoemaker WC, Appel PL, Kram HB, Bishop MH, Abraham E.

Sequence of physiologic patterns in surgical septic shock. *Crit Care Med* 1993; 21:1876-1889.

Schumacker PT.

Oxygen supply dependency in critical illness: an evolving understanding. *Intensive Care Med* 1998;24:97-99.

Segal HC, Hunt BJ, Cottam S, Downing A, Beard C, Francis JL, Potter D, Tan KC.

Fibrinolytic activity during orthotopic liver transplantation with and without aprotinin. *Transplantation* 1994; 58:1356-1360.



Sekiyama KD, Yoshiba M, Thomson AW.

Circulating proinflammatory cytokines (IL-1 $\beta$ , TNF- $\alpha$ , and IL-6) and IL-1 receptor antagonist (IL1-Ra) in fulminant hepatic failure and acute hepatitis. *Clin Exp Immunol* 1994; 98:71-77.

Selby AM, McCauley JC, Shell DN, O'Connell A, Gillis J, Gaskin KJ.

Indirect calorimetry in mechanically ventilated children: a new technique that overcomes the problem of endotracheal tube leak. *Crit Care Med* 1995; 23:365-370.

Sessler DI.

Mild perioperative hypothermia. *New Engl J Med* 1997; 336:1730-1737.

Shaw BW, Martin DJ, Marquez JM, Kang YG, Bugbee AC, Iwatsuki S et al.

Venous bypass in clinical liver transplantation. *Ann Surg* 1984; 200:524-533.

Sheffner AL.

The reduction in vitro in viscosity of mucoprotein solutions by a new mucolytic agent N-acetyl-L-cysteine. *Ann NY Acad Sci* 1963; 106:298-310.

Sheffner AL, Medler EM, Bailey KR, Gallo DG, Mueller AJ, Sarett HP.

Metabolic studies with N-acetylcysteine. *Biochem Pharmacol* 1966; 15:1523-1535.

Shibutani K, Komatsu T, Kubal K, Sanchala V, Kumar V, Bizzarri DV.

Critical level of oxygen delivery in anesthetized man. *Crit Care Med* 1983; 11:640-643.

Shibutani K, Muraoka M, Shirasaki S, et al.

Do changes in end-tidal PCO<sub>2</sub> quantitatively reflect changes in cardiac output? *Anesth and Analg* 1994; 79:829-833.

Shikora S, Bistran B, Borlase B, Blackburne G, Stone M, Benotti P.

Work of breathing: reliable predictor of weaning and extubation. *Crit Care Med* 1990; 18:157.

Skak C, Rasmussen A, Kirkegaard P, Secher NH.

Cerebral oxygen saturation and blood flow during liver transplantation. *Anesth Analg* 1997; 84:730-733.

Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH.

Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. *N Engl J Med* 1988; 319: 1557-1562.

Smilkstein MJ, Bronstein AC, Linden C, Augentein WL, Kulig KW, Rumack BH.

Acetaminophen overdose: a 48-hour intravenous N-acetylcysteine treatment protocol. *Ann Emerg Med* 1991; 20:1058-1063.

Smithies MN, Royston B, Makita K et al.

Comparison of oxygen consumption measurements: Indirect calorimetry versus the reversed Fick method. Crit Care Med 1991; 19:1401-1406.

Smithies M, Bihari DJ.

Delivery dependent oxygen consumption: asking the wrong questions and not getting any answers. Crit Care Med 1993; 21:1622-26.

Soni N, Fawcett WJ, Halliday FC.

Beyond the lung: oxygen delivery and tissue oxygenation. Anaesthesia 1993; 48:704-711.

Spanier TB, Klein RD, Nasraway SA, Rand WM, Rohrer RJ, Freeman RB, Schwaitzberg SD.

Multiple organ failure after liver transplantation. Crit Care Med 1995;23:466-473.

Spies CD, Reinhart K, Witt I, Meier-Hellmann A, Hannemann L, Bredle DL, Schaffartzik W.

Influence of N-acetylcysteine on indirect indicators of tissue oxygenation in septic shock patients: results from a prospective, randomised, double-blind study. Crit Care Med 1994; 2:1738-1746.

Steltzer H, Tuchy G, Hiesmayr M, Muller C, Germann P, Zimpfer M.

Peri-operative liver graft function: monitoring using the relationship between blood glucose and oxygen consumption during anaesthesia. Anaesthesia 1992; 47: 955-958.

Steib A, Freys G, Gohard R, Curzola U, Ravanello J, Lutun P, Boudjema K, Otteni J-C.

Tissue oxygenation during liver transplantation. Critical Care Medicine 1987; 20: 977-983.

Steib A, Saada A, Clever B, Lehmann C, Freys G, Levy S, Boudjema K.

Orthotopic liver transplantation with preservation of portocaval flow compared with venovenous bypass. Liver Transplantation and Surgery 1997; 3: 518-525.

Steib A, Freys G, Collin F, et al. Does N-acetylcysteine improve haemodynamics and graft function in liver transplantation? Liver Transplantation and Surgery 1998;4:152-157.

Stetz CW, Miller RG, Kelly GE, et al:

Reliability of the thermodilution method in the determination of cardiac output in clinical practice. Am Rev Respir Dis 1982; 126:1001-1004.

Stock MC, Ryan ME:

Oxygen consumption calculated from the Fick equation has limited utility. Crit Care Med 1996; 24:86-90.

Stratton HH, Feustel PJ, Newell JC.

Regression of calculated variables in the presence of shared measurement error.

Journal of Applied Physiology 1987;62:2083-2093.

Suter PM, Domenighetti G, Schaller M-D, Laverriere M-C, Ritz R, Perret C.

N-acetylcysteine enhances recovery from acute lung injury in man: A randomised, double-blind, placebo-controlled clinical study. Chest 1994; 105:190-194.

Svensson KL, Persson H, Henriksson BA, Karlberg I, Sonander H, Lundholm K, Stenqvist O, Schersten T.

Whole body gas exchange: amino acid and lactate clearance as indicators of initial and early allograft viability in liver transplantation. Surgery 1989; 105: 472-480.

Swinamer DL, Phang PT, Jones RL, Grace M, King EG.

Effect of routine administration of analgesia on energy expenditure in critically ill patients. Chest 1988; 92:4-10.

Takala J, Keinanen O, Vaisanen P, et al.

Measurement of gas exchange in intensive care: Laboratory and clinical validation of a new device. Crit Care Med 1989; 17:1041-1047.

Taskar V, John J, Larsson A, Wetterberg T, Jonson B.

Dynamics of carbon dioxide elimination following ventilator resetting. Chest 1995; 108: 196-202.

Thies JC, Koeppel TA, Lehmann T, Schemmer P, Otto G, Post S.

Efficacy of N-acetylcysteine as a hepatoprotective agent in liver transplantation: an experimental study. Trans Proc 1997; 29:1326-1327.

Thorens J-B, Jolliet P, Ritz M, Chevrolet J-C.

Effects of rapid permissive hypercapnia on hemodynamics, gas exchange, and oxygen transport and consumption during mechanical ventilation for the acute respiratory distress syndrome. Intensive Care Medicine 1996; 22: 182-191

Thrush D:

Spirometric versus Fick-derived oxygen consumption: which method is better?. Crit Care Med 1996; 24:91-95

Tissot S, Delafosse B, Bertrand O, et al.

Clinical Validation of the Deltatrac monitoring system in mechanically ventilated patients. Intensive Care Med 1995; 21:149-153.

Trey C, Davidson CS.

The management of fulminant hepatic failure. In: Popper H, Schaffner F, eds.

Progress in liver diseases. Vol III. New York: Grune and Stratton, 1970:282-298.

Tuchschmidt J, Fried J, Swinney R, Sharma OP.

Early hemodynamic correlates of survival in patients with septic shock. *Crit Care Med* 1989; 17:719-723

Tuchschmidt J, Fried J, Astiz M, Rackow E. Elevation of CO and oxygen delivery improves outcome in septic shock. *Chest* 1992;102:216-220.

Tzakis A, Todo S, Starzl TE.

Orthotopic liver transplantation with preservation of the inferior vena cava. *Annals of Surgery* 1989; 210: 649-652.

Tzakis AG, Reyes J, Nour B, Marino IR, Todo S, Starzl TE.

Temporary end to side portocaval shunt in orthotopic hepatic transplantation in humans. *Surg Gynecol Obstet* 1993; 176: 180-182.

Ultman JS, Burzstein S.

Analysis of error in the determination of respiratory gas exchange at varying FIO<sub>2</sub>. *J Appl Physiol* 1981; 50:210-216.

Uusaro A, Hartikainen J, Parviainen M, Takala J.

Metabolic stress modifies the thermogenic effect of dobutamine in man. *Crit Care Med* 1995; 23:674-680.

Vale JA, Proudfoot AT.

Paracetamol (acetaminophen) poisoning. *Lancet* 1995; 346:547-552. 14.

Vallet B, Chopin C, Curtis SE, Dupuis BA, Fourrier F, Mehdaoui H, LeRoy B, Rime A, Santre C, Herbecq P, Her B.

Prognostic value of the dobutamine test in patients with sepsis syndrome and normal lactate values: a prospective, multicentre study. *Crit Care Med* 1993; 21:1868-1875.

Viale J, Annat GJ, Bouffard Y, Delafosse B, Bertrand O, Motin J.

Oxygen cost of breathing in postoperative patients. Pressure support ventilation vs continuous positive airway pressure. *Chest* 1988; 93:506-509.

Vincent J, Roman A, De Backer D, Kahn RJ.

Oxygen uptake/supply dependency: Effects of short term dobutamine infusion. *Am Rev Respir Dis* 1990; 142:2-7.

Voerman H, Groeneveld J, de Boer H, Strack van Schijndel R, Nauta J, van der Veen E.

Time course and variability of the endocrine and metabolic response to severe sepsis. *Surgery* 1993; 114: 951-

Walley KR.

Mechanisms of decreased cardiac function in sepsis. In Vincent JL (ed) *Yearbook of intensive care and emergency medicine* 1996. Springer-Verlag, Berlin: 243-253.

Walley KR.

Heterogeneity of oxygen delivery impairs oxygen extraction by peripheral tissues: Theory. *J Appl Physiol* 1996; 81:885-894.

Walsh TS, Lee A.

Mathematical coupling in medical research: lessons from the oxygen kinetics literature. *Brit J Anaesth* 1998; 81:118-120

Watters J, Redmond M, Desai D, March R.

Effects of age and body composition on the metabolic response to elective colon resection. *Ann Surg* 1989; 21:213-

Webster NR, Bellamy MC, Lodge JPA, Sadek SA.

Haemodynamics of liver reperfusion: comparison of two anaesthetic techniques. *Anaesthesia* 1994; 72: 418-421.

Weissman C, Kemper M, Damask MC, Askanazi J, Hyman AI, Kinney JM.

Effect of routine intensive care interventions on metabolic rate. *Chest* 1984; 86:815-818.

Weissman C, Kemper M, Askanazi J, Hyman A, Kinney J.

Resting metabolic rate of the critically ill patient: measured versus predicted. *Anesthesiology* 1986; 64:673

Weissman C, Kemper M, Elwyn DH, Askanazi J, Hyman AI, Kinney JM.

The energy expenditure of the mechanically ventilated patient: an analysis. *Chest* 1986; 89:254-259.

Weissman C, Sardar A, Kemper M.

In vitro evaluation of a compact metabolic measurement instrument. *JPEN* 1990; 14:216-221.

Weissman C, Kemper M.

The oxygen uptake-oxygen delivery relationship during ICU interventions. *Chest* 1991; 99:430-435.

Weissman C, Kemper M.

Assessing hypermetabolism and hypometabolism in the postoperative critically ill patient. *Chest* 1992; 102: 1566-

Welch H, Pedersen P.

Measurement of metabolic rate in hyperoxia. *J Appl Physiol* 1981; 51:725-731.

Welte M, Pichler B, Groh J, Anthuber M, Jauch K-W, Pratschke E, Lenhart F-P, Haller M, Frey L, Peter K.

Perioperative mucosal pH and splanchnic endotoxin concentration in orthotopic liver transplantation. *British Journal of Anaesthesia* 1996; 76: 90-98.

Wendon J, Harrison P, Heaton N et al.

Serum nitrites and markers of postoperative morbidity. *Lancet* 1994; 344:411.

Wendon J, Harrison P, Keays R et al.

Effects of vasopressor agents and epoprostenol on systemic haemodynamics and oxygen transport in fulminant hepatic failure. *Hepatology* 1992;15:1067-1071.

Wendon JA, Harrison PM, Keays R, Williams R.

Cerebral blood flow and metabolism in fulminant liver failure. *Hepatology* 1994; 19:1407-1413.

Wigmore SJ, Walsh TS, Lee A, Ross JA.

Pro-inflammatory cytokine release and mediation of the acute phase protein response in fulminant hepatic failure. *Intensive Care Medicine* 1998; 24:224-229.

Williams PL, Warwick R (eds).

*Grays Anatomy* (36<sup>th</sup> Edition); Churchill Livingstone, London 1980.

Woda RP, Dzwonczyk RR, Orlowski JP, et al

Effect of measurement error on calculated variables of oxygen transport. *J Appl Physiol* 1996; 80:559-563.

Yu M, Levy MM, Smith P et al.

Effect of maximising oxygen delivery on morbidity and mortality in critically ill patients: a prospective randomised controlled study. *Crit Care Med* 1993;21:830-838.

Yu M, Takanishi D, Myers SA, Takiguchi SA, Severino R, Hasaniya N, Levy MM, McNamara JJ.

Frequency of mortality and myocardial infarction during maximising oxygen delivery: a prospective randomised trial. *Crit Care Med* 1995; 23:1025-1032.

Zeigler DW, Wright JG, Choban PS, Flancbaum L.

A prospective randomized trial of preoperative "optimisation" of cardiac function in patients undergoing elective peripheral vascular surgery. *Surgery* 1997; 122:584-592.

Zhang H, Spapen H, Nguyen DN, Benlabeled M, Buurman WA, Vincent J-L.

Protective effects of N-acetyl-L-cysteine in endotoxaemia. *Am J Physiol* 1994; 266:H1746-H1745.



**APPENDIX 1**

**COMMONLY USED FORMULAE AND EQUATIONS**

*Body Surface Area (BSA):*       $m^2$   
 $(\text{Height})^{0.725} \times (\text{Weight})^{0.425} \times 71.84 \times 10^{-4}$

*Cardiac Index (CI):*               $L.min^{-1}.m^{-2}$   
Cardiac output/BSA

*Systemic Vascular Resistance (SVR):*               $dynes.sec.cm^{-5}$   
 $[(\text{Mean arterial pressure}-\text{central venous pressure})/\text{cardiac index}] \times 80$

*Pulmonary Vascular Resistance (PVR):*               $dynes.sec.cm^{-5}$   
 $[(\text{Mean pulmonary artery pressure}-\text{pulmonary capillary wedge pressure})/\text{cardiac index}] \times 80$

*Oxygen delivery (DO<sub>2</sub>):*               $mL.min^{-1}$   
Cardiac output  $\times$  [(haemoglobin concentration  $\times$  1.34  $\times$  arterial oxygen saturation) +  
(0.003  $\times$  PaO<sub>2</sub>)]

## APPENDIX 2

### PRESENTATIONS MADE TO LEARNED SOCIETIES RELATED TO PRESENT WORK

January 1996

The effect of graft reperfusion on pulmonary haemodynamics, shunt and deadspace during orthotopic liver transplantation.

*Scottish Intensive Care Society, Stirling.*

March 1996

The Deltatrac metabolic monitor for measuring oxygen consumption during orthotopic liver transplantation.

*Anaesthetic Research Society, Nottingham.*

June 1996

Tissue oxygenation during liver transplantation: venovenous bypass vs the piggyback technique.

Energy expenditure in paracetamol-induced fulminant hepatic failure.

*Liver Intensive Care Group of Europe, Helsinki.*

September 1996

Oxygen consumption is independent of oxygen delivery following N-acetylcysteine in patients with fulminant hepatic failure.

The haemodynamic effects of N-acetylcysteine are shortlived in patients with fulminant hepatic failure.

*European Congress on Intensive Care, Glasgow.*

March 1997

Comparison between reverse Fick and indirect calorimeter measurements of oxygen consumption in patients with fulminant hepatic failure.

*Anaesthetic Research Society, Leicester.*

September 1997

Oxygen consumption following portal vein or hepatic artery reperfusion during liver transplantation.

*European Congress on Intensive Care, Paris.*

September 1998

Energy expenditure in fulminant hepatic failure

*European Congress on Intensive Care, Stockholm.*

## APPENDIX 3

### PUBLICATIONS TO DATE RELATED TO PRESENT WORK

Walsh TS, Hopton P, Lee A.

A comparison between indirect calorimetry and The Fick method for determining oxygen consumption in patients with fulminant hepatic failure.

*Critical Care Medicine*. 1998; **26**: 1200-1207.

Walsh TS, Hopton P, Philips B, Mackenzie SJ, Lee A.

The effect of N-acetylcysteine on oxygen kinetics in patients with fulminant hepatic failure.

*Hepatology*. 1998; **27**: 1332-1340.

Wigmore SJ, Walsh TS, Lee A, Ross JA.

Proinflammatory cytokine release and regulation of the acute phase protein response in fulminant hepatic failure.

*Intensive Care Medicine*. 1998; **24**: 224-229.

Walsh TS, Lee A.

Mathematical coupling in medical research: lessons from oxygen kinetics studies (Editorial).

*British Journal of Anaesthesia*. 1998; **81**: 118-120.

Walsh TS, Hopton P, Lee A.

The effect of graft reperfusion on haemodynamics and gas exchange during liver transplantation.

*British Journal of Anaesthesia*. 1998, **81**: 311-316.